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[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* **55**, 661 (1933).

[2] J. R. Goldsmith and D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* **7**, 221 (1955).

[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds* Vol. II, p. 239. Pergamon Press, London (1956).

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g kg mm cm ml cc cm^3 sec min hr n_D^{25} $[\alpha]_D^{25}$ 25° (without C which is always understood) but m.p., b.p., l. (litre), in. (inch) but in^2.

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VOL.
7
1959

LIST OF CONTENTS

VOLUME 7

NUMBERS 1/2

B. Eistert und F. Geiss: Spektroskopische Studien an „trans-fixierten" β-Diketonen und an cyclischen Malonsäure-estern 1

S. A. Barker, J. S. Brimacombe, A. B. Foster, D. H. Whiffen and G. Zweifel: Aspects of stereochemistry—II. Intramolecular hydrogen bonding in some monohydroxy derivatives of tetrahydrofuran tetrahydropyran and 1:3-dioxan 10

A. K. Barua and S. Pattabi Raman: Triterpenoids—X. The constitution of albigenic acid—a new triterpenoid sapogenin from *Albizzia lebbeck* Benth. 19

G. Gaudiano, A. Quilico and A. Ricca: Poly-*iso*oxazoles 24

F. Scheinmann and H. Suschitzky: Studies in the xanthone series—IV. Preparation and reactions of 2-allyl-1-hydroxyxanthone 31

Carl Djerassi and S. Burstein: Terpenoids—XXXIX. Iresin (Part 5). Complete structure and absolute configuration 37

S. M. Kupchan, W. S. Johnson and S. Rajagopalan: The configuration of cevine 47

Ken'ichi Takeda, Tokuo Kubota and (in part) Ariyoshi Shimaoka: Studies on the steroidal components of domestic plants—XIX. The structure of kogagenin, a sapogenin from *Dioscoria tokoro*, Makino 62

J. Harley-Mason and A. H. Laird: Isolation and structure of the fluorescent substances formed in the oxidative reaction of adrenaline and noradrenaline with ethylene-diamine 70

M. L. Dhar and T. R. Seshadri: Ring-isomeric change in isoflavones. Synthesis of 5,7-dimethoxy-6-hydroxyisoflavone, muningin and 5,7-dihydroxy-6-methoxyisoflavone 77

J. B. Hendrickson: Stereochemical implications in sesquiterpene biogenesis . 82

R. Gay et A. Horeau: Structure moléculaire et activité oestrogene—XVII. Comparison des configurations absolues des acides bisdéhydrodoisynolique normal et α, α-diméthyl β-éthyl allénolique physiologiquement actifs . . 90

L. van Hove: Contribution à l'étude des alcaloïdes de l'Holarrhéna Congolensis Stapf. Structure de l'hollarrhénine 104

Ryuji Tachikawa: Synthesis of some isoquinoline derivatives 118

C. H. DePuy, R. W. King and D. H. Froemsdorf: Pyrolytic elimination of acetates. Isotope effect, relative reactivity and mechanism 123

R. H. Mazur and J. A. Cella: 16-Substituted steroids 130

A. Bowers, L. Cuéller Ibáñez and H. J. Ringold: Steroids—CXX. Synthesis of halogenated steroid hormones. New routes to 6α-fluorotestosterone and the 6α- and 6β-fluoro analogs of progesterone. The synthesis of 6α- and 6β-fluoro Reichtein's Compound "S" and 6α- and 6β-fluorodesoxycorticosterone acetate 138

A. Bowers, E. Denot, M. Blanca Sanchez and H. J. Ringold: Steroids—CXXI. Synthesis of halogenated steroid hormones. 6α-Fluoro cortical hormones a new class of powerful corticoids 153

Addendum to Vol. 6, No. 2

F. Micheel: 1:6-Anhydro-D-galactose (Galactose α(1,5)β(1,6)) . . 163

J. G. TRAYNHAM and O. S. PASCUAL: Effects of ring size on the reactions of cyclic olefins. Halohydrins from methylenecycloalkanes 165
N. L. WENDLER, D. TAUB and R. P. GRABER: Group transfer and ring contraction phenomena in the D-homosteroid series 173
TOMOKICHIRO FUJISAWA and SHIGEHIKO SUGASAWA: Extension of the Bischler–Napieralski reaction—IV. Synthesis of some pyridine derivatives . . 185
F. W. LAMPE and F. H. FIELD: Reactions of ions with molecules in the gas phase 189
C. C. LEE, R. TKACHUK and G. P. SLATER: Rearrangement studies with ^{14}C—VIII. External and internal returns in the solvolysis of 2-phenyl-1-^{14}C-ethyl *p*-toluenesulfonate 206
M. J. S. DEWAR and VED P. KUBBA: New heteroaromatic compounds—IV. The nitration and chlorination of 10-methyl-10:9-borazarophenanthrene . 213
V. GALÍK, F. PETRŮ und J. KUTHAN: Zur Konstitution der Sandarakopimarsäure—II. Über die sterische Beziehung der Sandarakopimarsäure zu den Dextropimarsäuren 223
EIJI OCHIAI und MASAYUKI ISHIKAWA: Synthese von Derivaten der Cinchona-Alkaloide—XXXII. Synthese von Dihydrocorynanthean und 3-Epidihydrocorynanthean aus Cinchonin 228
R. P. GANDHI, O. P. VIG and S. M. MUKHERJI: Terpenoids—VI. A novel unambiguous synthesis of DL-ar-turmerone 236
A. J. BIRCH, R. W. RICHARDS, H. SMITH, A. HARRIS and W. B. WHALLEY: Studies in relation to biosynthesis—XXI. Rosenonolactone and gibberellic acid 241
P. W. KENT and P. C. J. BRUNET: The occurrence of protocatechuic acid and its 4-O-β-D-glucoside in *Blatta* and *Periplaneta* 252
A. CHATTERJEE, S. BOSE and C. GHOSH: Rhetsine and rhetsinine. The quinazoline alkaloids of *Xanthoxylum rhetsa* 257
L. H. BRIGGS, R. C. CAMBIE and J. L. HOARE: Chemistry of the podocarpaceae—III. A new lignan, seco-isolariciresinol and further constituents of the heartwood of *Podocarpus spicatus* 262
L. H. BRIGGS, R. C. CAMBIE, R. N. SEELYE and A. D. WARTH: Chemistry of the podocarpaceae—IV. Constituents of the heartwood of *Podocarpus dacrydioides* A. Rich. 270
B. CLEVERLEY and P. P. WILLIAMS: Polymorphism in substituted barbituric acids 277
J. CASON, J. SEARING FESSENDEN and C. L. AGRE: Location of a branch in a saturated carbon chain 289
W. COCKER, W. J. DAVIS, T. B. H. MCMURRY and P. A. START. Furan tetracarboxylic acid 299
J. W. POWELL and M. C. WHITING: The decomposition of sulphonylhydrazone salts—I. Mechanism and stereochemistry 305
S. F. BIRCH, T. V. CULLUM, R. A. DEAN and D. G. REDFORD: Sulphur compounds in the kerosine boiling range of Middle East distillates. Occurrence of a bicyclic thiophene and a thienyl sulphide 311
Erratum 319

VOL.
7
1959

Tetrahedron, 1959, Vol. 7, pp. 1 to 9. Pergamon Press Ltd. Printed in Northern Ireland

SPEKTROSKOPISCHE STUDIEN AN „TRANS-FIXIERTEN" β-DIKETONEN UND AN CYCLISCHEN MALONSÄURE-ESTERN

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Institut für Organische Chemie der Universität des Saarlandes, Saarbrücken

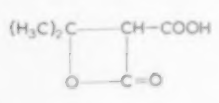
VOL. 7 1959

(*Received* 11 *January* 1959)

Zusammenfassung—Es wird der IR- und UV-spektroskopische Nachweis der Abhängigkeit des Keto–Enol–Gleichgewichts vom Lösungsmittel und des Enol–Enolat–Gleichgewichts vom pH für „trans-fixierte" β-Diketone vom Typus des *Dimedons* bestätigt. Cyclische Malonsäure ester vom Typus der *Meldrum*-Säure (*Iso*propylidenmalonat) sind in festem Zustand und in OH-gruppenfreien Solventien nicht enolisiert; in Methanol wurde nur die UV-Bande des Enolat-Anions gefunden, die bei Verringerung des pH-Wertes reversibel verschwindet, ohne dass eine der undissoziierten Enolform zuzuordnende Bande auftritt. Einer Hypothese, dass das Keto–Enol–Gleichgewicht „trans-fixierter" β-Dicarbonylverbindungen lösungsmittel-unabhängig sei, wird auf Grund experimenteller Gegenbeweise widersprochen.

Abstract—IR and UV spectra have confirmed that in "trans-fixed" β-diketones of the dimedone (methone) type, keto–enol–equilibrium depends on the solvent, and the enol–enolate–equilibrium on the pH. Cyclic malonic esters of the type of Meldrum's acid (*iso*propylidene malonate) are not enolized either in the solid state or in solvents free of OH-groups; in methanol only the UV band of the enolate anion was found, which on diminishing the pH disappeared reversibly without the appearance of band associated with the undissociated enol form. An hypothesis that keto–enol–equilibrium of "trans-fixed" β-dicarbonyl compounds is independent of the solvent has been disproved experimentally.

DIE von Meldrum[1] durch Kondensieren von *Malonsäure* mit *Aceton* in einem Gemisch aus konz. Schwefelsäure und Acetanhydrid erhaltene farblose Verbindung vom Schmp 96°, der er wegen ihrer sauren Natur die Formel I einer β-Lacton-carbonsäure



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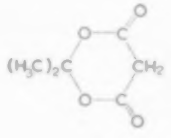
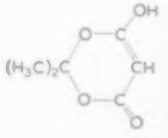
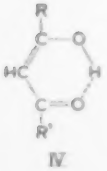


IIa



IIb



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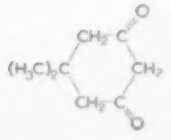
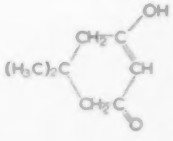


IIIa



IIIb

[1] A. Meldrum, *J. Chem. Soc.* **93**, 593 (1908).

zuerteilte, wurde von Davidson und Bernhard[2] eindeutig als *cyclischer Ester* der Malonsäure, IIa, erkannt. Die verhältnismässig hohe Acidität dieses Iso*propyliden-malonats* erklärte man, wie die des analogen carbocyclischen *Dimedons* III a damit, dass derartige „trans-fixierte" β-Dicarbonylverbindungen[3] in OH-gruppenhaltigen Lösungsmitteln, wie Wasser oder Methanol, weitgehend enolisiert seien; die Enolformen II b bzw. III b ihrerseits seien weitgehend in H^+ und Enolat-Anionen dissoziiert, weil hier, im Gegensatz zu den Enolformen „*cis*-fixierter" oder „frei-drehbarer" β-Dicarbonylverbindungen, das Enol-Proton nicht durch Chelatisierung (z.B. gemäss IV) festgehalten wird.

Wir haben uns in Weiterverfolgung der früher[4] mitgeteilten Versuche und Überlegungen seit 1955 eingehend mit „*Meldrums* Säure" und analogen Verbinddungen beschäftigt[5] und teilen hier einige Ergebnisse mit, zumal sich inzwischen auch andere Arbeitskreise[6] diesem Gebiet zugewandt haben. Insbesondere kondensierten wir Malonsäure und an der CH_2-Gruppe substituierte Malonsäuren mit einigen *alicyclischen* Ketonen, wobei *Malonsäure-spiro*-cyclo*alkyliden- Ester* vom Typus V entstanden.

Wir werden über die Herstellung und eine Reihe chemischer Umsetzungen von Meldrums Säure II und ihren spiro-Analogen V an anderer Stelle berichten. Hier sollen nur IR- und UV-spektroskopische Befunde mitgeteilt und diskutiert werden, die im Zusammenhang mit einer Publikation, die kürzlich in dieser Zeitschrift erschien,[7] allgemeineres Interesse finden könnten.

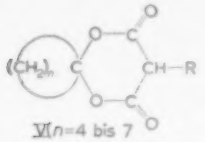
Erst nach Abschluss unserer Versuche wurden wir darauf aufmerksam, dass die Kondensation von Malonsäure mit *Cyclo*-pentanon und -hexanon bereits von Kandiah[8] beschrieben wurde. Er erhielt Produkte vom gleichen Schmelzpunkt wie wir, formulierte sie jedoch, gemäss der ursprünglichen Auffassung von Meldrum[1] und späterer Bearbeiter der Meldrum-Säure[9,10] als „1-Hydroxy-*cyclo*pentan-1-malonolacton" bezw. „1-Hydroxy*cyclo*hexan-1-malonolacton". Wegen dieser Bezeichnungen entgingen sie uns zunächst in der Literatur. Die den Formeln von Kandiah entsprechenden „β-Lactoncarbonsäuren" oder „Alkylhydroxy-malonolactone" sind also vorerst aus der Literatur zu streichen.

Auch Wulfsson[11] hat, offenbar in Unkenntnis der Publikation von Kandiah, Malonsäure mit *Cyclo*-hexanon kondensiert und das erhaltene Produkt, das allerdings nicht ganz rein war (er gab als Schmelzpunkt 84 bis 85° statt 94° an) als β-Lactoncarbonsäure aufgefasst.

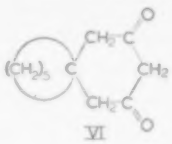
Kabachnik und Mitarbeiter[7] haben im Rahmen ihrer Publikation u.a. auch UV-Spektren von C-Methyl- und C-Äthylmalonsäure-*iso*propylidenester, also von C-Monoalkylderivaten von II, mitgeteilt und sie zur Stützung ihrer Hypothese benützt, dass das Keto–Enol–Gleichgewicht „trans-fixierter" β-Dicarbonylverbindungen lösungsmittel-*unabhängig* sei. Diese Hypothese steht im Widerspruch zu

[2] D. Davidson und S. Bernhard, *J. Amer. Chem. Soc.* **70**, 3428 (1948); E. Corey, *J. Amer. Chem. Soc.* **74**, 5897 (1952); D. Hurd und S. Hayao, *J. Amer. Chem. Soc.* **76**, 5563 (1954).
[3] B. Eistert und W. Reiss, *Chem. Ber.* **87**, 92 (1954).
[4] B. Eistert und W. Reiss, *Chem. Ber.* **87**, 108 (1954).
[5] F. Geiss, Diplomarbeit Darmstadt 1956, und Dissertation Saarbrücken 1958.
[6] H. R. Snyder und C. W. Kruse, *J. Amer. Chem. Soc.* **80**, 1942 (1958); P. J. Scheuer und S. G. Cohen, *Ibid.* 4933.
[7] M. I. Kabachnik, S. T. Yoffe und K. V. Vatsuro, *Tetrahedron* **1**, 317 (1957).
[8] A. Kandiah, *J. Chem. Soc.* 1226 (1932).
[9] E. Ott, *Liebigs Ann.* **401**, 159 (1913); O. Diels, R. Beckmann und G. Tönnies, *Ibid.* **439**, 76 (1924); A. Michael und J. Ross, *J. Amer. Chem. Soc.* **55**, 3684 (1933).
[10] N. S. Wulfsson und M. Schemjakin, *Dokl. Akad. Nauk SSSR* **29**, 206 (1940); **30**, 812 (1941); *J. Allgem. Chem. Russ.* **20**, 425 (1950).
[11] N. S. Wulfsson, *J. Allgem. Chem. Russ.* **20**, 425 (1950).

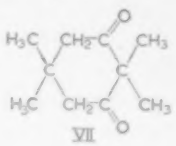
unseren Experimenten[3,4] und zu denen anderer Arbeitskreise.[12] Um dies zu begründen, müssen wir zunächst kurz auf die älteren und einige neue IR- und UV-spektroskopische Befunde am *Dimedon* und an seinem spiro-Analogen VI eingehen.



V (n=4 bis 7, R=H, CH_3 oder C_2H_5)



VI



VII

Das IR-Spektrum des *festen* spiro-5,5-Pentamethylen-*cyclo*hexan-dions-(1,3) VI zeigt sowohl bei der Aufnahme als KBr-Pressling (s. Abb. 1) wie auch in Tripenund

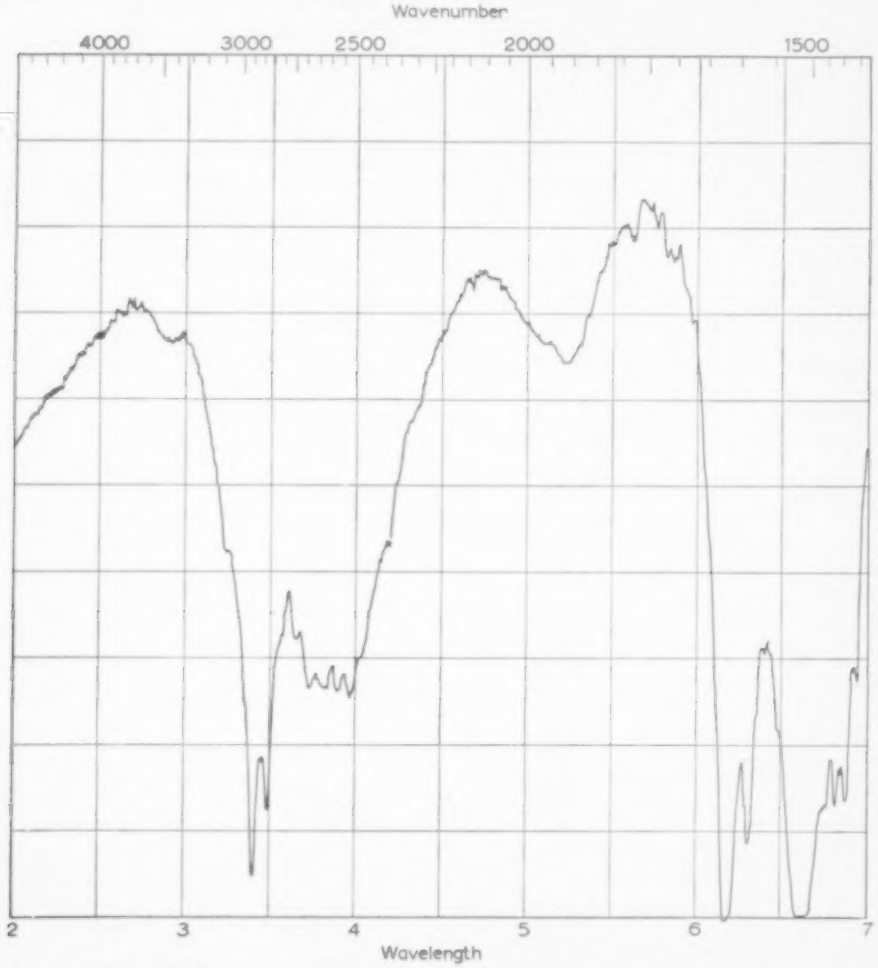


Abb. 1. Ausschnitt aus dem IR-Spektrum des 5·5-spiro-Pentamethylen-*cyclo*hexan-dions-(1·3) VI (KBr-Pressling).

[12] R. S. Rasmussen, D. D. Tunnicliff und R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1069 (1949); L. A. Duncanson, *J. Chem. Soc.* 1207 (1953).

VOL. 7 1959

Paraffin-mull ausser CH-Banden bei 3,36 und 3,45 μ eine Reihe kleiner Maxima zwischen 3,6 und 4,1 μ. Diese sind nach Rasmussen und Mitarbb,[12] die $CHCl_3$-Lösungen von Dimedon III gemessen haben, *enolischen* OH-Gruppen zuzuschreiben, deren Frequenz infolge zwischenmolekularer Assoziation mit CO-Gruppen benachbarter Molekeln ähnlich stark (und in mehreren verschiedenen Beträgen) verschoben sind wie die von OH-Gruppen fester Carbonsäuren, die bekanntlich[13] ebenfalls einen breiten Absorptionsbereich mit kleinen Spitzen im gleichen Gebiete besitzen. Ausserdem findet man in Abb. 1 zwei starke Banden bei 6,2 und 6,3 μ, die für α,β-ungesättigte Ketone charakteristisch sind. Die spiro-Verbindung VI liegt also, ebenso wie das Dimedon, im festen Zustande als *Enol-Form* (analog IIIb) vor. In Chloroform-Lösung tritt beim Dimedon ausser den genannten Banden noch eine Doppelbande mit Spitzen bei 5,80 und 5,875 μ auf, woraus zu schliessen ist,[12] dass die Lösung neben der Enolform IIIb „a good proportion" der Diketo-Form III a enthält.

Tatsächlich ergaben Messungen von Werner[14] am 3·3·5·5-*Tetra-methyl*-cyclo*hexan-dion*-(1·3)VII, das nicht enolisieren kann, ebenfalls eine Doppelbande bei 5,78 bzw. 5,875 μ und keine Banden zwischen 3,6 und 4,1 μ.

Der Nachweis, dass „trans-fixierte" β-Diketone, die im festen Zustande als Enole vorliegen, in hydrophoben Solventien ketisieren, wurde auch UV-optisch erbracht.[3] Löst man die spiro-Verbindung VI in *n*-Heptan, dann findet man bei raschem Arbeiten u.U. noch ein Maximum geringer Höhe, doch verschwindet dieses nach kurzer Zeit: Es bildet sich aus der hydrophilen Enol- die hydrophobere Diketo-Form. Das Keto–Enol–Gleichgewicht der trans-fixierten β-Diketone vom Typus VI und III ist also stark vom Lösungsmittel abhängig, und zwar umgekehrt wie das der „*cis*-fixierten" und der „frei-drehbaren" β-Diketone, bei denen die Enol-Form gemäss IV chelatisieren kann und dadurch hydrophober als die Diketo-Form wird.[15]

In OH-gruppenhaltigen Lösungsmitteln (Wasser, Methanol, Äthanol) lösen sich „trans-fixierte" β-Diketone III oder VI ohne merkliche Ketisierung. Man findet jedoch, abhängig vom pH-Wert des Lösungsmittels, eine *Kurvenschar*, die recht genau durch einen iso*bestischen Punkt* geht.[4] Beim Dimedon III, dessen Aciditätskonstante ($p_K = 5{,}2$) von der gleichen Grössenordnung ist wie die bei UV-optischen Messungen benützten Konzentrationen (ca. 10^{-4} bis 10^{-5} molar), ist die Kurve, infolge mehr oder weniger grosser Dissoziation der Enol-Form, konzentrationsabhängig.[4] Abbildung 3 zeigt UV-Absorptionskurven der Verbindung VI in „saurem" (d.h. Spuren HCl enthaltendem), in „gewöhnlichem" und in „basischem" (d.h. eine Spur Alkali enthaltendem) Methanol. Die „Enolat"-Bande liegt erwartungsgemäss bei längeren Wellen und ist auch höher als die „Enol"-Bande; in „gewöhnlichem" Methanol, in welchem ein Gemisch von Enol und Enolat vorliegt, ist die Bande breiter und tiefer, geht aber nahezu durch einen gemeinsamen *iso*bestischen Punkt.

Wir untersuchten nun die *cyclischen Malonsäureester* II und V nach den gleichen Methoden.

Das im KBr-Pressling oder in Tripen-Mull aufgenommene IR-Spektrum von Meldrums Säure II, zeigt, wie inzwischen von anderer Seite[6] mitgeteilt wurde, ebenso wie die von uns aufgenommenen IR-Spektren von Verbindungen von Typus V (s.

[13] M. St. C. Flett, *J. Chem. Soc.* 962 (1951); M. L. Josien und N. Fuson, *C. R. Acad. Sci., Paris* **235**, 1025 (1952); M. M. Davies und G. B. B. M. Sutherland, *J. Chem. Phys.* **6**, 755 (1938).
[14] Zitiert bei B. Eistert und W. Reiss, *Chem. Ber.* **87**, 102 (1954).
[15] N. V. Sidgwick, *J. Chem. Soc.* 907 (1925).

Abb. 2) zwischen 3,6 und 4,2 μ keine Banden, dagegen eine extrem kurzwellige *Doppelbande* bei 5,60 und 5,68 μ. Diese cyclischen Ester der Malonsäure liegen also im festen Zustande in der „Diketo"-Form II a vor, d.h. als nicht-enolisierte Ester bzw. δ-Lactone (Gesättigte δ-Lactone besitzen eine Bande bei 5,75 μ[16]). Auch in $CHCl_3$- und Tetrahydrofuran-Lösung fanden wir nur die CO-Doppelbande.

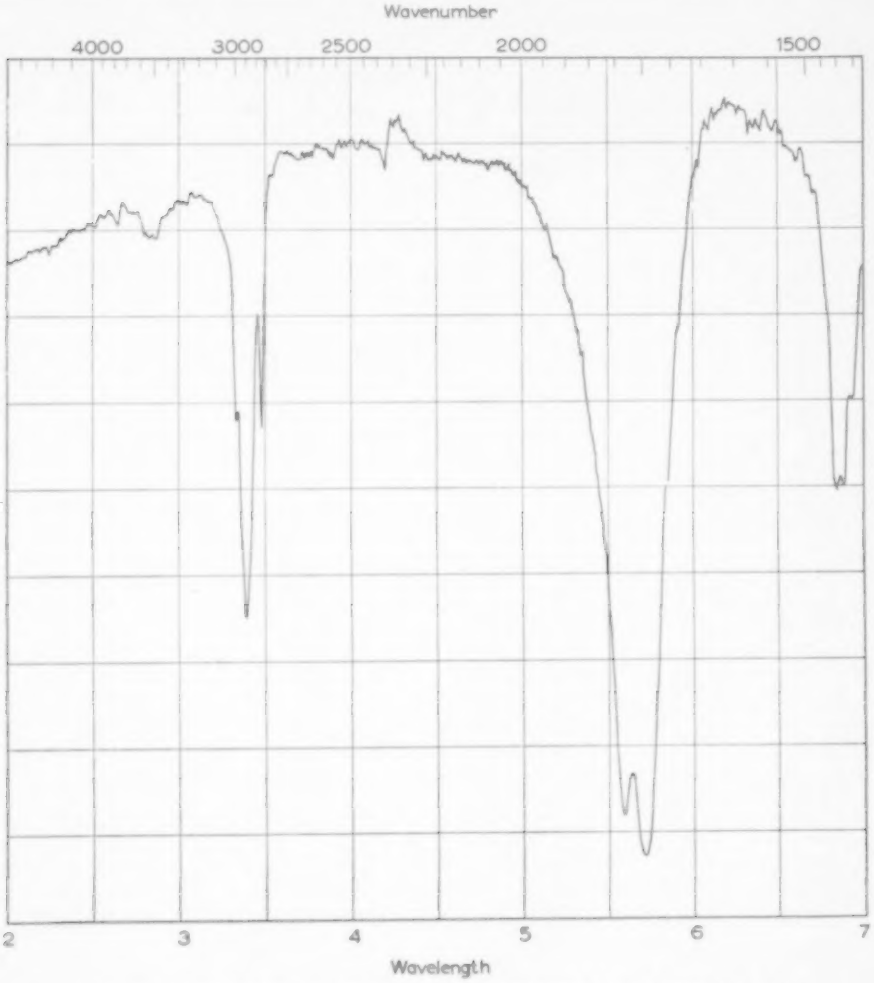


Abb. 2. Ausschnitt aus dem IR-Spektrum des Cycloheptyliden-malonats V($n = 6$) (KBr-Pressling).

Erwartungsgemäss zeigte sich auch in den UV-Spektren von Hexan-Lösungen der cyclischen Malonsäureester keine Enol-Bande.

Als wir jedoch Meldrums Säure II oder ihre spiro-Analogen V in *Methanol* lösten, fanden wir, wenn überhaupt, stets *ein* Maximum, das sowohl in „gewöhnlichem" wie in „basischem" Methanol bei der *gleichen* Wellenlänge lag und jeweils nur *verschieden*

[16] R. S. Rasmussen und R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1073 (1949).

hoch war; bei Zugabe von Spuren HCl-Gas verschwand es völlig, um bei Zugabe von Spuren Alkali wieder an der ursprünglichen Stelle aufzutauchen (s. Abb. 4).

Aus der stets gleichen Wellenlänge des Maximums und dessen Verschwinden ohne *iso*sbestischen Punkt folgt, dass man es hier, im Gegensatz zu den Verhältnissen bei den trans-fixierten *β-Diketonen* (Abb. 3), nicht mit einem pH-abhängigen Gleichgewicht zwischen zwei Chromophor-Systemen zu tun hat, sondern mit der reversiblen

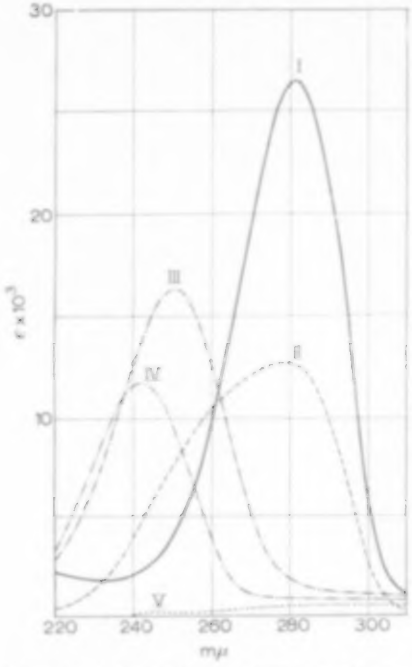
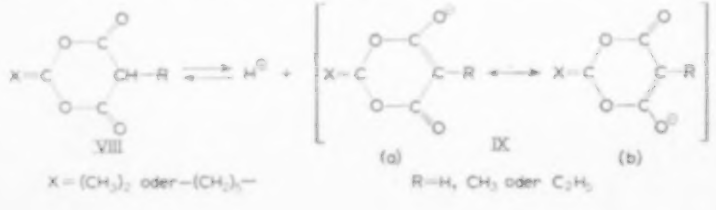


ABB. 3. UV-Spektren des 5·5-spiro-Pentamethylen-cyclohexan-dions-(1·3) VI
($c = 2{,}5 \cdot 10^{-5}$ mol/l.).
I in „basischem" Methanol
II in „gewöhnlichem" Methanol
III in „saurem" Methanol
IV in Äther
V in Isooktan

Umwandlung eines Chromophors in eine in jenem Wellenlängenbereich nicht absorbierende Verbindung. Da die Bande in „basischem" Methanol am höchsten ist, muss der in Abbildung 4 gezeigte Chromophor das Enolat-*Anion* IX a↔b des cyclischen Malonsäureesters sein. Das Auftreten der freien, undissoziierten Enol-Form (z.B. IIb) ist UV-spektroskopisch mit unseren Mitteln nicht nachweisbar.



Man kommt also zu dem Schluss, dass die in festem Zustande und in hydrophoben Solventien als „Diketo-Formen" VIII vorliegenden cyclischen Ester der Malonsäure auch in OH-gruppenhaltigen Lösungsmitteln (Methanol) in der „Diketo-Form" VIII gelöst sind, wenn man durch Zugabe von Spuren HCl ihre Dissoziation hintanhält, und dass diese „Diketo-Form" ohne Zwischenbildung nachweisbarer Mengen Enolform sich unmittelbar mit ihren mesomeren Enolat-Anionen IX a↔b in ein pH-abhängiges Gleichgewicht setzt. Während wir bei den trans-fixierten *β-Diketonen* ein von der Natur des Lösungsmittels abhängiges Gleichgewichtssystem zwischen den

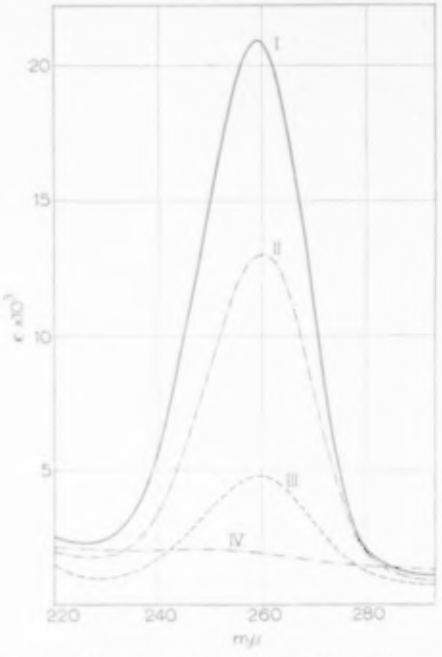


Abb. 4. UV-Spektren des Cycloheptyliden-malonats ($c = 2{,}5 \cdot 10^{-5}$) V ($n = 6$).
I in „basischem" Methanol
II in „gewöhnlichem" Methanol
III in Methanol mit sehr geringen Mengen HCl-Gas
IV in HCl-haltigem Methanol und in Isooktan

drei Komponenten Diketon und Enolform bzw. Enolform und Enolat nachwiesen,[3,4] lässt sich bei den cyclischen *Malonsäureestern* nur ein Gleichgewicht zwischen „Diketo-Form" und *Enolat*-Anion nachweisen.

Analoge Befunde ergaben sich bei unseren Untersuchungen von C-Mono-alkyl-Derivaten V (R = CH_3 oder C_2H_5).

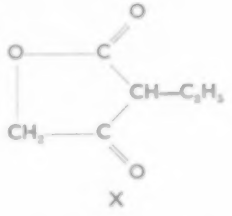
Die cyclischen Malonsäureester II bzw. V sind also „*Pseudosäuren*". Ihre relativ grosse Acidität (Meldrums Säure: p_{K_S} ca. 5,2) beruht, wie die der Carbonsäuren oder des Dimedons, darauf, dass das *mesomere Anion eine relativ kleine Proton-Affinität besitzt*: sie ist aber kein *Beweis* dafür, dass der Dissoziation der Pseudo-Säure II a bzw. VIII eine Umlagerung in die Enolform (IIb) vorausgeht.[17]

[17] F. Arndt, *Statische und dynamische Acidität* Vol. VIII, p. 1. Abhandlungen der Braunschweigischen Wissenschaftl. Ges. (1956).

Mit anderen Worten: Sie besagt nichts über den Sitz des „sauren" Protons in der undissoziierten Verbindung.

Auf der Grundlage der oben dargelegten experimentellen Befunde seien nun die von Kabachnik und Mitarbb[7] mitgeteilten UV-Spektren der „C-Methyl-" und „C-Äthyl-Meldrumsäure" besprochen. Die Autoren liessen die Messungen nur in Methanol und in Äthanol ausführen. Die Kurven (l.c.S. 323) zeigen Maxima bei ca. 372 mμ, also infolge der bathochromen Wirkung der C–Alkyl–Substitution, die wir auch beim C–Methyl–dimedon antrafen,[6] bei etwas längeren Wellen als die unsubstituierte Meldrum-Säure in den gleichen Lösungsmitteln. Die Extinktionshöhen sind in allen vier Kurven nahezu gleich; in Äthanol jedoch jeweils etwas niedriger als in Methanol.

Nach unseren obigen Befunden handelt es sich nicht um die Absorption der freien Enolformen, sondern um die der *Enolat-Anionen* IX der cyclischen Ester der C–Akyl–malonsäuren in den beiden Alkoholen. Da die Dielektrizitätskonstanten von Methanol und Äthanoll nur wenig voneinander verschieden sind (31,2 bzw. 25,8 für reine wasserfreie Alkohole; i. allgem. enthalten sie jedoch Spuren Wasser), ist es nicht verwunderlich, dass die cyclischen Malonsäureester in den hochverdünnten Lösungen (ca. 10^{-5} molar), wie sie bei UV-Messungen üblich sind, nahezu gleiche Mengen *Enolat-Anionen* IX a$\leftrightarrow$b enthalten. Die von den russischen Autoren mitgeteilten UV-Spektren können also nicht als Hinweis auf eine lösungsmittelunabhänigige *Enol*isierung der cyclischen Malonsäureester gewertet werden. Das gleiche gilt für die von ihnen mitgeteilten UV-Spektren der Äthyltetronsäure X in Wasser, Methanol und Äthanol.



X

Da die russischen Kollegen[7] unseren oben nochmals dargelegten spektroskopischen Nachweis der Lösungsmittel-Abhängigkeit der Keto–Enol–Gleichgewichte „trans-fixierter" β-Dicarbonylverbindungen ohne stichhaltige Begründung als „doubtful" ansahen [sie nehmen an, dass sich bei unseren Messungen in „saurem" Methanol *Methyläther* der Enolformen gebildet hätten, die bei ungefähr gleichen Wellenlängen absorbieren wie die freien Enolformen[18]] glaubten sie, aus neuen *Bromtitrationen* einwandfreie Aufschlüsse über die von ihnen vermutete Lösungsmittel-Unabhängigkeit des Keto–Enol–Gleichgewichts der „trans-fixierten" β-DiCarbonylverbindungen erhalten zu können. Um die Fehlerquelle auszuschalten, die durch die Weiter-Enolisierung der zunächst entstehenden Monobrom-Verbindungen gegeben ist, titrierten sie C–*Monoalkyl*–Derivate des Dimedons, der Tetronsäure und der Meldrum-

[18] Die Enolmethyläther der „trans-fixierten" β-Diketone absorbieren zwar bei praktisch der gleichen Wellenlänge wie die freien Enolformen, aber mit weniger hohen Extinktionen. Selbst wenn sich in der methanolischen Lösung unter der Einwirkung von Spuren HCl teilweise Enolmethyläther bildete, wäre die davon verschiedene Absorption in „gewöhnlichem" und in „basischem" Methanol und das Auftreten des *iso*sbestischen Punktes damit nicht erklärt. Unseren spektroskopischen Nachweis der Ketisierung in Heptan-Lösung übergehen die russischen Autoren völlig.

Säure, deren Monobrom-Derivate ja nicht mehr enolisieren können. Sie fanden dabei tatsächlich für jede untersuchte Verbindung untereinander nahezu gleiche Bromverbrauchs-Werte, unabhängig davon, ob sie die genannten Verbindungen in Methanol, in Chloroform, in Äthanol oder (soweit löslich) in Benzol gelöst hatten. Sie sehen darin den endgültigen Beweis für die von ihnen angenommene Lösungsmittel-Unabhängigkeit des Keto–Enol–Gleich-gewichts der „trans-fixierten" β-Dicarbonylverbindungen.

Dabei übersahen sie jedoch eine weitere, grundsätzliche Fehlerquelle der Bromtitrations-Methode, auf die auch Arndt[19] aufmerksam gemacht hat:

Bei der „direkten" Titration nach Meyer,[20] die die russischen Autoren anwandten, benützt man *alkoholische* (insbesondere methanolische) Brom-Lösungen, und man giesst die auf ihren Enol-Gehalt zu untersuchenden Lösungen auf jeden Fall vor der Titration in (tief gekühlten) Alkohol, wobei man unterstellt, dass sich das im ursprünglichen Lösungsmittel, z.B. Chloroform, vorhandene Gleichgewicht während der Titrations-Operationen nicht ändert. Diese Voraussetzung ist bei solchen Verbindungen, deren Enolformen chelatisiert sind (s. Formel IV), häufig erfüllt. Bei solchen Verbindungen jedoch, deren Enolform nicht chelatisiert sein kann, die also relativ stark sauer sind, ist die Umlagerungs-Geschwindigkeit der Keto- in die Enol-(bzw. Enolat-) Form wahrscheinlich so gross, dass ein „Einfrieren" des in dem ursprünglichen Lösungsmittel vorhandenen Gleichgewichts nicht möglich ist. Vielmehr stellt sich sofort dasjenige Gleichgewicht ein, welches dem nunmehr überwiegend vorhandenem Lösungsmittel (Methanol oder Äthanol) entspricht.[19]

Arndt hat diese Fehlerquelle der üblichen Bromtitrations-Methode zunächst an *β-Cyanketonen* festgestellt, deren Enol-Formen wegen des gestreckten Baues der CN-Gruppe keine Chelate bilden können und deshalb relativ sauer sind. Sie gilt naturgemäss auch für „trans-fixierte" β-Dicarbonylverbindungen, bei denen ja ebenfalls Enol*chelate* sterisch unmöglich sind. Es war deshalb ohne weiteres zu erwarten, dass bei der üblichen „direkten" Bromtitration der von den russischen Autoren untersuchten „trans-fixierten" Verbindungen stets annähernd der für *methanolische* Lösungen geltende Brom-Verbrauch gefunden wird, unabhängig davon, in welchem Solvens die untersuchten Verbindungen ursprünglich gelöst waren. Dabei entspricht der Brom-Verbrauch, wie aus Obigem zu ersehen, der in den methanolischen Lösungen vorhandenen Menge *Enolat* + Enol.

Damit dürfte die experimentelle Grundlage der weitgehenden theoretischen Folgerungen, die Kabachnik und Mitarbeiter[7] aus der vermeintlichen Lösungsmittel-Unabhängigkeit des Keto–Enol–Gleichgewichts „trans-fixierter" β-Dicarbonylverbindungen zogen, und die in einer speziellen Erweiterung der Meyerschen Gleichung[21] resultierten, in Frage gestellt, sein.

Die Verfasser danken der *Deutschen Forschungs-gemeinschaft* und dem *Fonds der Chemischen Industrie* für die Unterstützung ihrer Arbeiten.

[19] F. Arndt, I. Loewe und R. Ginkök, *Rev. Fac. Sci. Istanbul* (Ser. A. Tome XI) **4**, 161 (1946); *Chem. Abstr.* **41**, 3760.
[20] K. H. Meyer, *Ber. Dtsch. Chem. Ges.* **44**, 2720 (1911); *Liebigs Ann.* **380**, 212 (1911); G. Hesse und G. Krehbiel, *Liebigs Ann.* **593**, 35 (1955).
[21] K. H. Meyer, *Ber. Dtsch. Chem. Ges.* **47**, 826 (1914).

VOL. 7 1959

Tetrahedron, 1959, Vol. 7, pp. 10 to 18. Pergamon Press Ltd. Printed in Northern Ireland

ASPECTS OF STEREOCHEMISTRY—II*

INTRAMOLECULAR HYDROGEN BONDING IN SOME MONOHYDROXY DERIVATIVES OF TETRAHYDROFURAN, TETRAHYDROPYRAN AND 1:3-DIOXAN

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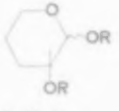
Abstract—The extent of intramolecular hydrogen bonding between hydroxyl groups and ring oxygens, as determined by infra-red spectroscopy in the hydroxyl stretching region, in a series of monohydroxy derivatives of tetrahydropyran, tetrahydrofuran and 1:3-dioxan provides direct experimental evidence for the stabilities of different conformations of certain of the alcohols. The synthesis of tetrahydropyran-3-ol is described and the mechanism of the reaction of perbenzoic acid with glycals is discussed.

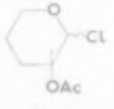
In addition to the intramolecular hydrogen bonding (bonding), which may occur between hydroxyl groups in dihydroxy derivatives of tetrahydropyran, bonding between suitably located hydroxyl groups and the ring oxygen is also possible and, as a result, conformational stability may by influenced. Observations and comments on this effect were reported in Part I. Bonding may also occur between each ring oxygen and the hydroxyl group in derivatives of 1:3-dioxan-5-ol (1:3-O-methylene-glyceritol) and determination of the extent of bonding has permitted an allocation of configuration[1] to *cis*- and *trans*-1:3-O-benzylidene-glyceritol (2-phenyl-1:3-dioxan-5-ol).

The extent of intramolecular hydrogen bonding in these compounds may be determined from the infra-red spectra of their dilute solutions in carbon tetrachloride.[2,3] Below a concentration of 0·005 M intermolecular hydrogen bonding is negligible and absorptions at ca. 3590 cm^{-1} and ca. 3620 cm^{-1} may be associated[2] with bonded and free hydroxyl groups respectively. The respective proportions of free and bonded hydroxyl groups may be approximately assessed from the extinction coefficients (ϵ) for the relative absorptions.

With the exception of tetrahydropyran-3-ol all the alcohols listed in Table 1 have been described in the literature. Tetrahydropyran-3-ol was prepared by the following route. Treatment of 2:3-dihydropyran with perbenzoic acid in wet ether furnished 2:3-dihydroxy-tetrahydropyran (I) which was isolated and purified as the diacetate (II). Reaction of the diacetate (II) with ethereal hydrogen chloride gave the chloro intermediate (III) which was converted to tetrahydropyran-3-ol (IV) by reduction with lithium aluminium hydride.



I, R = H
II, R = Ac



III

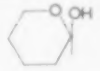
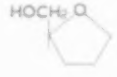
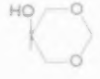
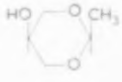
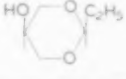
IV

* Part I, *Tetrahedron* **4**, 351 (1958).

[1] J. S. Brimacombe, A. B. Foster and M. Stacey, *Chem. & Ind.* 1228 (1958).
[2] L. P. Kuhn, *J. Amer. Chem. Soc.* **74**, 2492 (1952); *Chem. & Ind.* **76**, 4323 (1954).
[3] A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.* 4391 (1956).

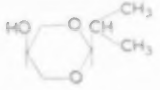
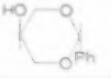
VOL. 7 1959

TABLE 1. INFRA-RED SPECTRAL DATA FOR CERTAIN ALCOHOLS
(Determined on solutions in carbon tetrachloride of concentration 0·005 M or less)

Alcohol	Structure[a]	Infra-red absorptions (cm^{-1})[b] Free OH(ε)	Bonded OH(ε)	$\Delta\nu$[c]	$\Delta\nu$[1,d]
Tetrahydropyran-2-ol (5-hydroxypentanal)		3620(40)	—		
Tetrahydropyran-3-ol		3620(40)	3604(50)	16	25
Tetrahydropyran-4-ol		3622(40)	—		
2-Hydroxymethyl-tetrahydropyran		—	3597(55)		
Tetrahydrofuran-2-ol (4-hydroxybutanal)		3619(40)	—		
Tetrahydrofuran-3-ol		3628(48)	—		
2-Hydroxymethyl-tetrahydrofuran (tetrahydrofurfuryl alcohol)		—	3600(47)		
1:3-Dioxan-5-ol (1:3-O-methylene glyceritol)		3635(21)	3594(100)	41	35
2-Methyl-1:3-dioxan-5-ol (1:3-O-ethylidene-glyceritol)		—	3593(50)		
2-Ethyl-1:3-dioxan-5-ol (1:3-O-propylidene-glyceritol)		—	3590(100)		

[a] Formula depicted to emphasize their relation with the carbohydrates.
[b] Values in parentheses are the relative extinction coefficients (ε).
[c] Arithmetical difference between free and bonded hydroxyl absorption frequencies.[2]
[d] Arithmetical difference between bonded and standard secondary hydroxyl (3629 cm^{-1}) absorption frequencies.[3]

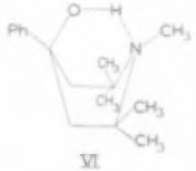
TABLE 1 (*Cont.*)

Alcohol	Structure[a]	Infra-red absorptions (cm^{-1})[b] Free OH(ϵ)	Bonded OH(ϵ)	$\Delta\nu$[c]	$\Delta\nu$[1,d]
2-Isopropyl-1:3-dioxan-5-ol (1:3-O-isobutylidene-glyceritol)		—	3589(55)		
cis-2-Phenyl-1:3-dioxan-5-ol (1:3-O-benzylidene-glyceritol)[e]		—	3593(78)		
trans-2-Phenyl-1:3-dioxan-5-ol[e]		3633(55)	3593(70)	40	36

[a] Data taken from ref. 1.

In Table 1 are recorded the infra-red absorption frequencies determined on solutions of 0·005 M or less of the alcohols in dry carbon tetrachloride. As would be expected from a consideration of accurate scale models, bonding does not occur in the tetrahydrofuran-2 and 3-ols or in the tetrahydropyran-2 and 4-ols. Intramolecular hydrogen bonding is theoretically possible in the boat conformation (V) of tetrahydropyran-4-ol but it appears that bonding is too weak to hold the molecule in such an unfavoured conformation. Bonding has been observed[4] in a related 6-membered ring compound in a boat conformation namely 4-hydroxy-1:2:2:6:6-pentamethyl-4-phenyl-piperidine (VI). In this case the alternative chair conformations are destabilized by the *gem*-dimethyl groups.

V



VI

Tetrahydrofuran-2-ol and tetrahydropyran-2-ol may be regarded as equilibrium mixtures of the cyclic forms and the respective acyclic structures 4-hydroxybutanal and 5-hydroxypentanal. The infra-red spectra of liquid films of the two alcohols showed weak carbonyl absorptions[5] at 1726 and 1724 cm^{-1} respectively, indicative of the presence of a small percentage of the acyclic forms. A similar inference could be drawn from the spectra of solutions of the two alcohols in carbon tetrachloride at concentrations of 10·0 mg/ml which showed the following absorptions: tetrahydrofuran-2-ol 1730 cm^{-1} ($\epsilon = 31$), tetrahydropyran-2-ol 1720 cm^{-1} ($\epsilon = 22$). Typical aliphatic aldehydes[5] show carbonyl absorption in the range 1720–1740 cm^{-1} and have[6] carbonyl extinction coefficients (ϵ) ca. 700 ± 100 so that in the present cases about 4 per cent of the alcohols are in the open chain form. This is the same

[4] R. E. Lyle, *J. Org. Chem.* **22**, 1280 (1957).
[5] L. J. Bellamy, *Infra-red Spectra of Complex Molecules* p. 133. Methuen (1956).
[6] R. E. Richards and W. R. Burton, *Trans. Faraday Soc.* **45**, 874 (1949).

order of magnitude as found by Hurd and Saunders[7] from ultra-violet measurements on solutions of the alcohols in aqueous dioxan.

In view of the low percentage of molecules of tetrahydrofuran-2-ol and tetrahydropyran-2-ol which exist in the open chain form, any bonding between the hydroxyl group and the carbonyl oxygen in the acyclic structures would be difficult to detect. However, it seems unlikely that such bonding would occur since the formation of seven or eight membered rings would be required.

In carbon tetrachloride solution the hydroxyl groups in 2-hydroxymethyl-tetrahydropyran and 2-hydroxymethyl-tetrahydrofuran appear to be completely bonded. In the latter case bonding involves the formation of a bicyclic system structurally related to *cis*-bicyclo [3.3.0] octane. A similar bicyclic system would be formed by bonding in 1:2-O-isopropylidene-glyceritol. However, in carbon tetrachloride solutions of this cyclic acetal, a significant percentage of the hydroxyl groups are not bonded as shown by the absorptions at 3647 cm^{-1} ($\epsilon = 25$, free hydroxyl) and 3608 cm^{-1} ($\epsilon = 49$, bonded hydroxyl). From a study of accurate scale models it appears that the *gem*-dimethyl groups in the isopropylidene residue may sterically hinder the approach of the hydroxyl group to the relevant ring oxygen and hence limit intramolecular hydrogen bonding.

VOL. 7 1959

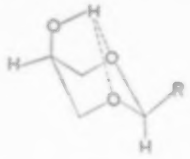
An examination of models also suggests that bonding could occur in both chair conformations of 2-hydroxymethyl tetrahydropyran. If the hydroxymethyl group is axial then the bicyclic system formed by bonding is structurally related to *cis*-hydrindane (*cis*-bicyclo [4.3.0] nonane) and if equatorial to *trans*-hydrindane. Although the available evidence does not indicate which configuration predominates, by analogy with the hydrindanes, for which combustion data indicates[8] the *trans*-form to be most stable, and on the basis of the principles of conformational analysis[9] 2-hydroxymethyl-tetrahydropyran would be expected to assume a chair conformation with the hydroxymethyl group in an equatorial position.

On the reasonable assumption[9,10] that the tetrahydropyran ring normally exists in the chair conformation then the presence of both free and bonded hydroxyl groups in carbon tetrachloride solutions of tetrahydropyran-3-ol may be interpreted as indicating the presence of an equilibrium of both chair conformations (Fig. 1). Bonding can occur only in the chair conformation with an axial hydroxyl group and the relative extinction coefficients (40 and 50) for free and bonded hydroxyl groups indicates approximately, equal proportions. Some stabilization of the conformation with an axial hydroxyl group must be conferred by bonding since, from the principles of conformational analysis,[9] the hydroxyl group would otherwise adopt predominantly an equatorial position. Pickering and Price[11] have concluded that for *cyclo*hexanol in carbon disulphide solution approximately 65 per cent of the molecule exists in the chair conformation with an equatorial hydroxyl group.

Introduction of a second ring oxygen as in 1:3-dioxan-5-ol permits more efficient bonding of an axially located hydroxyl group than in tetrahydropyran-3-ol (Fig 2). The relative extinction coefficients (21 and 100) for free and bonded hydroxyl groups in 1:3-dioxan-5-ol indicates that the equilibrium of chair conformations now strongly

[7] C. D. Hurd and W. H. Saunders, *J. Amer. Chem. Soc.* **74**, 5324 (1952).
[8] W. Hückel, *Liebigs Ann.* **533**, 1 (1938).
[9] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956).
[10] J. A. Mills, *Adv. Carbohydrate Chem.* **10**, 1 (1955).
[11] R. A. Pickering and C. C. Price, *J. Amer. Chem. Soc.* **80**, 4931 (1958).

favours that with an axial hydroxyl group. Further, the introduction of a suitably oriented substituent on to C_2 in 1:3-dioxan-5-ol, as for example the phenyl group in *cis*-1:3-O-benzylidene-glyceritol (VII), effectively fixes the conformation and permits



VII, R=Ph
VIII, R=CH_3
IX, R=C_2H_5
X, R=$^iC_3H_7$

complete bonding (Table 1). This is not the case with the *trans*-isomer[1] in which an appreciable percentage of the hydroxyl groups are not bonded (Table 1). By comparison with these results 1:3-O-ethylidene-glyceritol[12] (VIII), 1:3-O-propylidene-glyceritol[13] (X), and 1:3-O-isobutylidene-glyceritol[13] the spectra of which (Table 1) show absorptions for bonded hydroxyl groups only, may be tentatively assigned the *cis*-structures.[14]

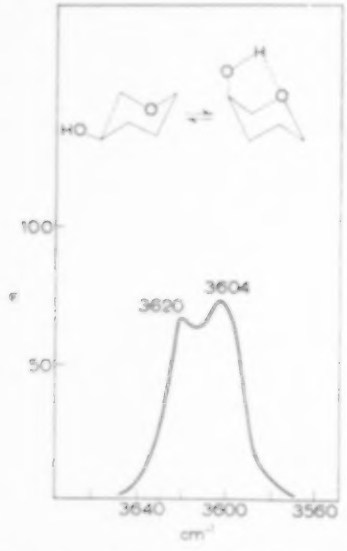


Fig. 1. Infra-red spectrum in CCl_4 solution at ca. 0·005 M concentration of tetrahydropyran-3-ol. The spectrum is consistent with the equilibria shown assuming that the molecules exist preferentially in the chair forms.[10]

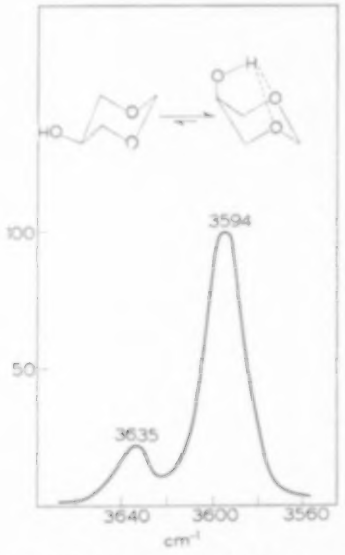
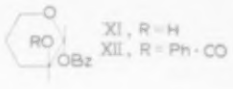


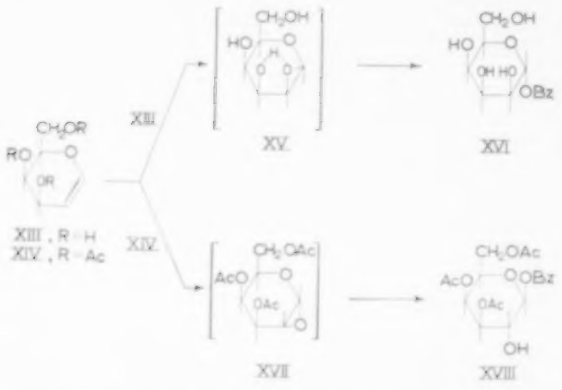
Fig. 2. Infra-red spectrum in CCl_4 solution at ca. 0·005 M concentration of 1:3 dioxan-5-ol. The spectrum is consistent with the equilibria shown assuming that the molecules exist preferentially in the chair forms.[10]

During the investigation of the synthesis of tetrahydropyran-3-ol a possible route via reduction of 2:3-epoxy-tetrahydropyran (2:7-dioxabicyclo [4.1.0] heptane) was examined but proved to be unsuitable since, under the experimental conditions used, the epoxide, if formed, underwent further reaction. For example, treatment of 2:3-dihydropyran with perbenzoic acid in dry chloroform gave a diol monobenzoate.

[12] H. S. Hill, A. C. Hill and H. Hibbert, *J. Amer. Chem. Soc.* **50**, 2243 (1928).
[13] S. M. Trister and H. Hibbert, *Canad. J. Res.* **14**[B], 415 (1939).
[14] N. Baggett and A. B. Foster, unpublished results.

This compound may be tentatively allocated the structure *trans*-2-benzoyloxy-3-hydroxy-tetrahydropyran (XI) on the basis of a close parallel with the results of Wood and Fletcher[15] who showed that oxidation of D-galactal (XIII) with perbenzoic acid gave 1-O-benzoyl-α-D-talopyranose (XVI). It is of interest that, in the latter reaction, D-galactose derivatives are not formed so that if the reaction proceeds via the intermediate epoxide (XV) it is highly stereospecific. On the other hand perbenzoic acid





reacts[16] with 3:4:6-tri-O-acetyl-D-galactal (XIV) to yield 3:4:6-tri-O-acetyl-1-O-benzoyl-β-D-galactopyranose (XVIII) presumably via the intermediate epoxide (XVII). Henbest and Wilson[17] have shown that peracids oxidize cyclohex-2-enol (XIX, R = H) to the *cis*-epoxide (XX) whereas the acetate (XIX, R = Ac) reacts more slowly but

yields mainly the *trans*-epoxide (XXI). The stereospecificity of the former reaction is considered to be due to intramolecular hydrogen bonding in the transition state whereas in the latter reaction the bulk of the acetoxy group may block one side of the double bond. The parallelism between the reactions in the respective D-galactal and cyclohex-2-enol series is clear if the former proceed through the intermediate epoxides (XV) and (XVII). Since, in the D-galactal series an enol ether not an olefin is initially involved, then the occurrence of further reaction is not surprising. A similar reaction sequence occurs in the D-glucal series. Thus D-mannose is the main product[18] of the reaction of D-glucal and perbenzoic acid in the presence of water

[15] H. B. Wood and H. G. Fletcher, *J. Amer. Chem. Soc.* **79**, 3234 (1957).
[16] P. A. Levene and R. S. Tipson, *J. Biol. Chem.* **93**, 631 (1931).
[17] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.* 1958 (1957).
[18] M. Bergmann and H. Schotte, *Ber.* **54**, 440 (1921); B. Helferich, *Adv. Carbohydrate Chem.* **7**, 209 (1952).

whereas the peracid reacts with 3:4:6-tri-O-acetyl-D-glucal to yield[19] predominantly 3:4:6-tri-O-acetyl-1-O-benzoyl-D-glucose. D-Glucose derivatives predominate when either 3-O-methyl or 3:4:6-tri-O-methyl-D-glucal is treated with perbenzoic acid in the presence of water.[19] In conflict with this general pattern of reactions is the observation[19] that mainly D-mannose derivatives result from the action of perbenzoic acid on 3:4:6-tri-O-acetyl-D-glucal in the presence of water. The epoxide (XVII) [3:4:6-tri-O-acetyl-1:2-anhydro-α-D-glucopyranose (Brigl's anhydride)] postulated as an intermediate in the reaction of 3:4:6-tri-O-acetyl-D-galactal (XIV) with perbenzoic acid has been obtained[20] by another route.

Benzoylation of the monobenzoate (XI) gave a dibenzoate with the possible structure *trans*-1:2-dibenzoyloxy-tetrahydropyran (XII). Treatment of the dibenzoate with ethereal hydrogen chloride followed by reduction with lithium aluminium hydride gave an inseparable mixture of benzyl alcohol and, presumably, tetrahydropyran-3-ol.

EXPERIMENTAL

With the exception of tetrahydropyran-3-ol the alcohols used in this paper are described in the literature. Table 2 contains the physical constants of and other data about the alcohols.

Actions of perbenzoic acid on 2:3-dihydropyran. 2:3-Dihydropyran (6 g) was added to a solution of perbenzoic acid (10 g) in dry chloroform (200 ml) at −5°. After 10 min the solution was extracted

Table 2. Physical constants of and other data about certain alcohols

Alcohol	Physical constants			
	b.p.	n (temp.)	b.p.[a]	n^{a} (temp)
Tetrahydropyran-2-ol (5-hydroxy-pentanal)[b,21]	50–52°/1 mm	1·4530 (22)	54–55°/3 mm[21]	1·4514 (25)[21]
Tetrahydropyran-3-ol	92–95° (bath)/ 12–15 mm	1·4571 (21)	—	—
Tetrahydropyran-4-ol[22]	85–88°/12 mm	1·4580 (20)	84–85°/12 mm[22]	1·4580 (20)[22]
2-Hydroxymethyl-tetrahydropyran[23]	95–96°/25 mm	1·4570 (20)	73–74·5°/11 mm[23b]	1·4582 (17)[23b]
Tetrahydrofuran-2-ol (4-hydroxy-butanal)[b,24,25]	70–72°/15 mm	1·4420 (22)	65°/12 mm[25]	1·4403 (20)[25]
Tetrahydrofuran-3-ol[26]	84–88°/24 mm	1·4507 (20)	82–88°/24 mm[26]	1·4497 (25)[26]
2-Hydroxymethyl-tetrahydrofuran (tetrahydrofurfuryl alcohol)	178–180°	1·4504 (20)		
1:3-Dioxan-5-ol (1:3-O-methylene-glyceritol)[27]	82°/11 mm	1·4533 (20)	82°/11 mm[27]	1·4533[27]
2-Methyl-1:3-dioxan-5-ol (1:3-O-ethylidene-glyceritol)[12]	40–45°/0·05 mm	1·5152 (21)	52°/2 mm[12]	1·4532 (17)[12]
2-Ethyl-1:3-dioxan-5-ol (1:3-O-propylidene-glyceritol)[13]	48°/0·01 mm	1·4490 (21)	50–51°/2 mm[13]	1·4448 (25)[13]
2-Isopropyl-1:3-dioxan-5-ol (1:3-O-isobutylidene-glyceritol)[13]	51–54°/ 0·01 mm	1·4785 (19)	55–56°/2 mm[13]	—

[a] Literature values.
[b] Reducing toward's Fehling's solution.

[19] P. A. Levene and A. L. Raymond, *J. Biol. Chem.* **88**, 513 (1930); C. Tanaka, *Bull. Chem. Soc. Japan* **5**, 214, (1930); *Chem. Zentr.* 2765 (1930, II).
[20] P. Brigl, *Z. Physiol. Chem.* **116**, 1 (1921); **122**, 245 (1922).
[21] L. E. Schniepp and H. H. Geller, *J. Amer. Chem. Soc.* **68**, 1646 (1948).
[22] O. Heuberger and L. N. Owen, *J. Chem. Soc.* 910 (1952).
[23] K. Alder and E. Ruder, *Ber.* **74**, 920 (1941); R. H. Hall, *J. Chem. Soc.* 1398 (1953).
[24] R. Paul, *Bull. Soc. Chim.* **8**, 911 (1941).
[25] R. Paul and S. Tchelitcheff, *Bull Soc. Chim.* **15**, 197 (1948).
[26] H. Wynberg, *J. Amer. Chem. Soc.* **80**, 364 (1958).
[27] H. Hibbert and N. M. Carter, *J. Amer. Chem. Soc.* **50**, 3120 (1928).

VOL. 7 1959

thrice with cold 2 N NaOH and finally with water. Evaporation of the dried (Na_2SO_4) chloroform solution and recrystallization of the residue from ether–light petroleum (60–80°) gave *trans* (?)-2-benzoyloxy-tetrahydropyran-3-ol m.p. 85–87°. (Found: C, 64·5; H, 6·0. $C_{12}H_{14}O_4$ requires: C, 64·8; H, 6·3%). The infra-red spectrum (Nujol mull) showed absorptions at 1703 and 1720 cm^{-1} (carbonyl) and at 3460 cm^{-1} (hydroxyl).

A solution of benzoyl chloride (4 g) in dry pyridine (20 ml) was added to a solution of the preceding monobenzoate (3·5 g) also in dry pyridine (20 ml) at 0°. After 30 hr at room temp the mixture was diluted with chloroform, and the chloroform solution washed successively with dilute hydrochloric acid, water, aqueous cadmium chloride (10%, w/v), water and aqueous sodium hydrogen carbonate. Evaporation of the dried (Na_2SO_4) chloroform solution and recrystallization of the residue from methanol gave *trans* (?)-2:3-dibenzoyloxy-tetrahydropyran (5 g) m.p. 70–75°. (Found: C, 69·9; H, 5·4. $C_{19}H_{18}O_5$ requires: C, 69·9; H, 5·5%). The infra-red spectrum (Nujol mull) showed absorptions at 1721 and 1736 cm^{-1} (carbonyl) but no absorption for free hydroxyl groups.

Tetrahydropyran-3-ol. 2:3-Dihydropyran (9 g) was added to a solution of perbenzoic acid (15 g) in aqueous saturated ether (200 ml) at 0°. After 24 hr the mixture was extracted with water and the aqueous extract was washed with a small amount of ether to remove benzoic acid and then evaporated at 40°/12–15 mm to yield crude 2:3-dihydroxy-tetrahydropyran. The diol was acetylated by treatment with dry pyridine (30 ml) and acetic anhydride (15 ml) at room temp for 48 hr. The mixture was poured into water and the solution extracted with chloroform. The combined extracts were washed successively with N HCl, aqueous cadmium chloride, and dilute aqueous sodium hydrogen carbonate. Evaporation of the dried (Na_2SO_4) chloroform solution and distillation of the residue gave 2:3-diacetoxy-tetrahydropyran as a colourless liquid b.p. 70–72° (bath)/0·1 mm, n^{20} 1·4458 (Found: C, 53·2; H, 7·0. $C_9H_{14}O_5$ requires: C, 53·5; H, 7·0%).

A solution of the diacetate (5 g) in ether (50 ml) which had been saturated with hydrogen chloride at 0° was kept at the same temp for 48 hr. The solution was then evaporated under diminished pressure and the remaining traces of hydrogen chloride were removed by repeated distillation of benzene from the residue. A solution of the syrupy product in ether containing lithium aluminium hydride (7·5 g) was boiled under reflux for 4 hr. Excess of lithium aluminium hydride was destroyed by the addition of water and the resultant precipitate was dissolved by the addition of a saturated aqueous solution of Rochelle salt. Exhaustive extraction of the solution with ether followed by evaporation of the extract and distillation of the residue gave tetrahydropyran-3-ol as a colourless liquid b.p. 92–95° (bath)/12–15 mm, n^{21} 1·4571 which was non-reducing towards Fehling's solution (Found: C, 58·95; H, 9·0. $C_5H_{10}O_2$ requires: C, 58·8; H, 9·8). Toluene-*p*-sulphonylation in the usual manner gave syrupy 3-toluene-*p*-sulphonyloxy-tetrahydropyran. (Found: C, 56·1; H, 6·4; S, 12·3. $C_{12}H_{16}O_4S$ requires: C, 56·2; H, 6·2; S, 12·5%). The infra-red spectrum (liquid film) was quite distinct from those of the isomeric tetrahydropyran-2- and 4-ols.

1:3-O-*Methylene-glyceritol* (1:3-*dioxan*-5-*ol*). A solution of 2-O-benzoyl-1:3-O-methylene-glyceritol (3 g, prepared according to the method of Hibbert and Carter[27]) in chloroform (20 ml) was treated with dry methanol (5 ml) to which a trace of metallic sodium had been added. After 24 hr at room temp neutralization was effected with solid carbon dioxide and the solution was evaporated. A solution of the residue in water was extracted firstly with light petroleum (60–80°) and then exhaustively with ether. Evaporation of the ether extract and distillation of the residue gave 1:3-O-methylene glyceritol, b.p. 80–85°/11 mm, n^{20} 1·4540. (Hibbert and Carter[27] quote b.p. 82°/11 mm, n^{20} 1·4533). Saponification of the benzoate using aqueous alkali according to the method of Hibbert and Carter[27] gave a product n^{20} 1·4541. The infra-red spectra (liquid film) of the two products were identical.

1:3-O-*Ethylidene-glyceritol* (2-*methyl*-1:3-*dioxan*-5-*ol*). Acetaldehyde (15 g) was passed into a mixture of glyceritol (34 g) and conc H_2SO (1·0 ml). The mixture was neutralized with solid K_2CO_3 and excess acetaldehyde was removed by extraction with light petroleum (60–80°). The residue was dissolved in ether, the solution washed with water and then evaporated to yield a residue from which a mixture (29 g) of O-ethylidene-glyceritols was obtained with b.p. 45–48°/0·05 mm. Benzoyl chloride (26 g) was added to a solution of the mixed O-ethylidene-glyceritols (25 g) in dry pyridine (100 ml). After 10 hr at 0° the mixture was worked up in the usual way to yield 5-benzoyloxy-2-methyl-1:3-dioxan m.p. 86° (Hill, Hill and Hibbert[12] quote m.p. 86° for the same compound prepared in a different manner). The behaviour of the benzoate on chromatography on alumina indicated that it was homogeneous.

Debenzoylation was effected with sodium methoxide in methanol as described above for 5-benzoyloxy-1:3-dioxan to yield 2-methyl-1:3-dioxan-5-ol, b.p. 40–45°/0·05 mm, n^{21} 1·5152; (Hill, Hill and Hibbert[12] quote b.p. 52°/2 mm, n_D^{17} 1·4532).

Infra-red spectra. These were measured in 2 cm layers in CCl_4 solution with a 2500 l. p.i. grating used in the fourth order on the spectrometer previously described.[28] Concentration of the diol was always approximately 0·005 M; the extinction coefficients, ϵ, are maximum values and are equal to $(1/cl)\log_{10}(I_0/I)$ with l in cm and c in moles/litre and are accurate to ± 10. The results are recorded in Table 1. It would be unwise to asssume that the extinction coefficients of bonded and free hydroxyl groups are identical either in one molecule or between molecules and so accurate values are not available for the proportion of each form. The extinction coefficients per hydroxyl group lie in the range 40–125 for compounds with hydroxyl groups which are free, bonded or with a proportion of each. This means that the ratio of bonded to free hydroxyl groups is approximately the ratio of the extinction coefficients but the variations are such that accurate values for each form cannot be obtained.

Acknowledgement—The authors thank Professor M. Stacey, F.R.S., for his interest in this work.

[28] H. Spedding and D. H. Whiffen, *Proc. Roy. Soc.* A **238**, 245 (1956).

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VOL. 7 1959

TRITERPENOIDS—X

THE CONSTITUTION OF ALBIGENIC ACID—A NEW TRITERPENOID SAPOGENIN FROM *ALBIZZIA LEBBECK* BENTH.

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(*Received* 20 *January* 1959)

Abstract—The constitution of albigenic acid—a new triterpenoid sapogenin from the beans of *Albizzia lebbeck* Benth., has been established as 3β:16α-dihydroxyolean-13(18)-en-28-oic acid and its partial synthesis from echinocystic acid is described.

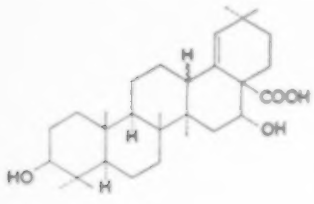
THE isolation of "albigenic acid" a new triterpene acid and echinocystic acid from the beans of *A. lebbeck* Benth., has been reported in an earlier communication.[1] Albigenic acid (Ia), $C_{30}H_{48}O_4$, gave a monomethyl ester (Ib), which formed a diacetate (Ic). It showed a violet → pink colouration in the Liebermann–Burchardt reaction. As albigenic acid was found to occur in association with echinocystic acid, which also has the same molecular formula, there seemed to be a close relationship between the two acids. Owing to its laevorotation, albigenic acid was thought to be a 3α-epimer of echinocystic acid, since it has generally been observed that the 3α-OH has a negative molecular rotatory contribution.[2] This possibility was overruled by the fact that the diketone obtained by the oxidation of methyl albigenate was different from methyl diketo echinocystate. Methyl diketoalbigenate gave a positive Zimmermann colour reaction proving the presence of 3-keto group.[3] Under comparable conditions the rate of hydrolysis of methyl albigenate was found to be almost the same as that of methyl echinocystate. The rate of hydrolysis of the triterpene esters of the oleanane series having the carboxyl group at the C_{17} position is usually very low whereas the presence of hydroxyl groups β to the carbomethoxyl group facilitates the hydrolysis.[3] That one of the hydroxyl groups is β to the carboxyl group is shown by the fact that methyl diketoalbigenate (VI) undergoes decarboxylation on saponification.

The fact that albigenic acid and its derivatives gave a pale yellow colouration with tetranitromethane and that methyl albigenate consumed only one mole of perbenzoic acid showed the presence of one double bond. The relative rapidity with which the uptake of perbenzoic acid was complete (24 hr) indicated that the ethylenic linkage in albigenic acid was not at the usual 12:13-position, in which case the consumption of the oxidant is very slow.[4] The double bond in albigenic acid, however, resisted hydrogenation under standard conditions in presence of platinum oxide catalyst and was not attacked by osmic acid. The rapid thermal decarboxylation of albigenic acid at its melting point indicated the possibility of the double bond being in the $\beta\gamma$-position to the carboxyl group, as $\beta\gamma$-unsaturated acids are known to be readily decarboxylated

[1] A. K. Barua and S. P. Raman, *Sci. and Cult.* **23**, 435 (1958).
[2] W. Klyne and W. M. Stokes, *J. Chem. Soc.* 1979 (1954).
[3] D. H. R. Barton and P. De Mayo, *J. Chem. Soc.* 887 (1954).
[4] L. Ruzicka, H. Silbermann and M. Furter, *Helv. Chim. Acta* **15**, 482 (1932).

on pyrolysis.[5] Albigenic acid, unlike oleanolic acid, neither lactonized nor formed a bromolactone, under conditions used for the formation of the derivatives of oleanolic acid.[6]

The first evidence bearing on the positions of the ethylenic double bond and the carboxyl group in albigenic acid came from the formation of a lactone diacetate identical with the 18-iso-echinocystic acid lactone diacetate (VII).



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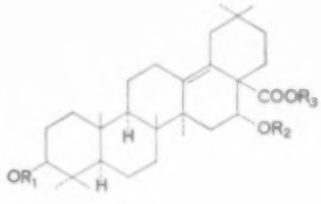
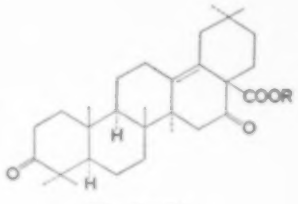
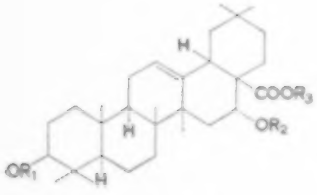


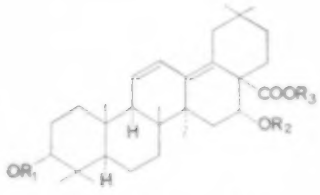
Ia, $R_1 = R_2 = R_3 = H$
Ib, $R_1 = R_2 = H$; $R_3 = CH_3$
Ic, $R_1 = R_2 = CH_3CO$; $R_3 = CH_3$
Id, $R_1 = CH_3CO$; $R_2 = H$; $R_3 = CH_3$



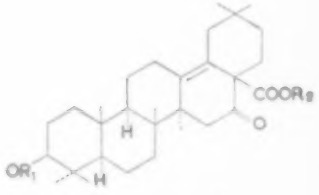
VI R = CH_3



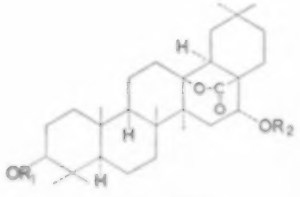
III $R_1 = R_2 = CH_3CO$
$R_3 = CH_3$



IVa, $R_1 = CH_3CO$; $R_2 = H$; $R_3 = CH_3$
IVb, $R_1 = R_2 = CH_3CO$; $R_3 = CH_3$



V $R_1 = CH_3CO$
$R_2 = CH_3$



VII $R_1 = R_2 = CH_3CO$

The above observations clearly show albigenic acid to be a dihydroxy pentacyclic triterpene acid of the oleanane series with the carboxyl group at the usual C_{17} position and closely related to echinocystic acid having the structure Ia or II. In order to decide between these structures, the compound (Ic) was prepared from echinocystic acid on the following lines. Oxidation of diacetyl methyl echinocystate (III) with

[5] D. H. R. Barton and C. J. W. Brooks, *J. Chem. Soc.* 257 (1951).
[6] A. Winterstein and G. Stein, *Z. physiol. Chem.* **199**, 56, 64 (1931).

selenium dioxide in glacial acetic acid furnished IVa which showed triple ultra-violet absorption maxima at 244, 252 and 260·5, (log ε 4·4, 4·44, 4·26) typical of the $\Delta^{11:12,\ 13:18}$ dienes of the β-amyrin series.[5,7] Hydrogenation of this diene gave Id, which on acetylation furnished albigenic ester diacetate (Ic).

It is evident that in the formation of IVa from III the 16-acetyl group is eliminated. This is proved by the fact that Id on oxidation gave a keto compound V, which gives no colour in the Zimmermann reaction indicating the absence of a 3-keto group.[3] This clearly establishes the validity of the structures IVa, V and Id assigned to the respective compounds. The glassy mass obtained as one of the selinium dioxide oxidation products, on hydrogenation yielded diacetyl methyl albigenate (Ic) and hence should have the structure IVb. On the basis of this unequivocal partial synthesis the structure and stereochemistry of albigenic acid must be represented by Ia. The molecular rotation difference in the case of albigenic acid and echinocystic acid is $-249°$ which is, however, far below the observed value for the shift of the double bond from 12:13- to 13:18-position in the oleanane series. (cf. δ-oleanolic acid,[8] δ-amyrin,[9] and δ-erythrodiol.)[5]

We believe that the recently reported[10] discrepancy in the properties of echinocystic acid isolated from the seeds of *A. lebbeck* Benth., is due to the non-homogeneity of the compound since we have observed that it is very difficult to separate echinocystic acid from this source, from the closely allied albigenic acid, the isolation of which has not been reported by the previous workers. We also encountered oleanolic acid in the sapogenin mixture.

That albigenic acid is not an acid-induced isomerization product[11] of echinocystic acid is borne out but the fact that echinocystic acid itself in model experiments was found to be unaffected under the conditions of the isolation process. Albigenic acid, incidentally, is the first example of a naturally occurring triterpene acid with the double bond at the more thermodyanamically stable 13:18-position and therefore is of biogenetic interest.

EXPERIMENTAL*

Isolation of sapogenins. Air-dried powdered beans of *A. lebbeck*† Benth. containing the seeds (1·5 kg) were Soxhleted for 50 hr with alcohol (90%) and the viscous dark brown residue, left on evaporation of the solvent *in vacuo*, was repeatedly washed with ether (5 × 500 cc). The brown ether insoluble gummy mass, which gave characteristic tests for saponins, was dissolved in alcohol (1 l., 70%) and refluxed for 4 hr after addition of conc HCl (200 cc). The alcohol was evaporated over a steam bath, the volume being kept constant by addition of water. The chocolate-coloured crude sapogenin thus obtained was extracted in a Soxhlet apparatus with ether for 40 hr and the ether extract washed with aqueous caustic soda (2%, 5 × 200 cc). The alkali washings on neutralization gave a voluminous white precipitate, (12·5 g).

* The m.p.s are uncorrected and were determined in a bisulphate bath. Optical rotations are in chloroform solutions unless otherwise specified. Ultra-violet spectra were measured in ethanol solutions with a Beckmann DU instrument. Brockmann's alumina (E. Merck) was used for chromatography and acid washed alumina refers to Brockmann's alumina deactivated with 5% of 10% acetic acid. Petroleum ether, b.p. 60–80°, was used for chromatography.

† We wish to thank Dr. S. K. Mukherjee, Keeper, Central National Herbarium, Sibpur, Calcutta, for botanical identification of the plant material.

[7] L. Ruzicka, G. Muller and H. Schellenberg, *Helv. Chim. Acta* **22**, 767 (1939).
[8] L. Ruzicka and O. Jegger, *Helv. Chim. Acta* **24**, 1236 (1941).
[9] O. Jegger, J. Norymberski and L. Ruzicka, *Helv. Chim. Acta* **27**, 1532 (1944).
[10] Ch. Sannie, H. Lapin and I. P. Varshney, *Bull. Soc. Chim. Fr.* 1440 (1957).
[11] G. Brounlie, M. B. E. Fayez, F. S. Spring, R. Stevenson and W. S. Strachan, *J. Chem. Soc.* 1377 (1956).

Methyl albigenate (Ib). The above acid sapogenin fraction was esterified in the usual way using excess diazomethane in ether solution and a benzene solution of the crude ester was adsorbed over a column of acid-washed alumina (400 g). Petroleum ether eluate (600 cc) gave a fraction which on several crystallizations from methanol gave a compound (1 g), $C_{31}H_{50}O_3$, m.p. 199–200°, $[\alpha]_D^{30}$ +73°, which showed no change in m.p. when admixed with an authentic sample of methyl oleanolate. Eluting the column with petroleum ether–benzene mixture (3 : 1, 20 l.) gave solids of m.p. 203–207°, (7 g), which on crystallization from methanol yielded needles, $C_{31}H_{50}O_4$, m.p. 212–214°, $[\alpha]_D^{30}$ +33·5° (ethanol 95%). This was shown to be identical with methyl echinocystate by direct comparison with an authentic sample.* Further elution of the column with the same solvent mixture (1 : 1, 5 l.) gave crystals, m.p. 219–224°, (0.9 g), which on repeated crystallizations from methanol furnished methyl albigenate (Ib), m.p. 225–226°, $[\alpha]_D^{27}$ −10°, (Found: C, 76·3, 76·73; H, 10·08, 10·45; OMe, 6·8; M.W. (Rast's) 480, 491; $C_{31}H_{50}O_4$ requires: C, 76·49; H, 10·35; OMe, 6·37% M.W. 486). Methyl albigenate in chloroform solution consumed exactly 1 mole of perbenzoic acid in 24 hr and there was no further uptake for 15 days. The ester could be recovered unchanged from its acetic acid solution after shaking for 12 hr, in an atmosphere of hydrogen in presence of platinum oxide catalyst at room temp and atmospheric pressure. The ester was also quantitatively recovered after treatment with osmic acid in dry ether or pyridine solution for 7 days at room temp.

Albigenic acid (Ia). Methyl albigenate (500 mg) was refluxed with an alcoholic solution of caustic potash (20%, 50 cc) for 3 hr and yielded an acidic fraction (68%) which on crystallization from chloroform methanol mixture gave albigenic acid (Ia), m.p. 246–248 (dec),† $[\alpha]_D^{31}$ −13° (ethanol). (Found: C, 75·99; H, 10·02; Eq. Wt. 468, 470. $C_{30}H_{48}O_4$ requires: C, 76·22; H, 10·24%; Eq. Wt. 472). The acid on esterification gave methyl albigenate (Ib). The neutral fraction obtained after saponification was found to be unreacted methyl albigenate. The rate of hydrolysis of methyl echinocystate under identical conditions was 62%. Albigenic acid in chloroform solution gave a pale yellow colouration with tetranitromethane and was recovered unchanged after treatment adequate for the formation of a lactone or bromolactone of oleanolic acid.[8]

Diacetyl methyl albigenate (Ic). Methyl albigenate (Ib, 500 mg) was heated with pyridine (5 cc) and acetic anhydride (5 cc) over a steam bath for 3 hr and a benzene solution of the product passed through a column of alumina (50 g). Benzene–petroleum ether (1 : 1, 250 cc) eluted fractions which crystallized from rectified spirit to give diacetyl methyl albigenate as plates, (Ic, 420 mg), m.p. 189–190°, $[\alpha]_D^{27}$ −54°. (Found C, 74·0; H, 9·68; AC, 13·98; $C_{35}H_{54}O_6$ requires: C, 73·64; H, 9·53; Ac, 15·04%). It gave a pale yellow colour with tetranitromethane in chloroform solution and on mild hydrolysis (5% alcoholic caustic potash) gave methyl albigenate.

Methyl diketoalbigenate (VI). A cold solution of methyl albigenate (Ib, 300 mg) in pyridine (10 cc) was added slowly to a slurry of chromium trioxide–pyridine complex[12] (from 400 mg of CrO_3 and 10 cc of pyridine) at −15°, and the mixture kept at room temp for 24 hr after which it was poured into crushed ice. The separated solids were filtered, washed repeatedly with hot water and dried. The product after adsorption over acid washed alumina (50 g) using benzene, was eluted by benzene–petroleum ether mixture (2 : 1, 200 cc) and on repeated crystallization from methanol gave the diketo-ester (VI) as sharp needles, m.p. 207–209°, $[\alpha]_D^{29}$ −156° (dioxane), λ_{max} 294 mμ (log ε 2·14). (Found: C, 77·16; H, 9·82. $C_{31}H_{46}O_4$ requires: C, 77·13; H, 9·61%). This compound gave a yellow colouration with tetranitromethane and a violet colour in the Zimmermann test. Mixed m.p. with an authentic sample of methyl diketoechinocystate (m.p. 167–168°) was 138–156°.

The diketoester (VI, 200 mg) did not furnish any acidic material on refluxing for 8 hr with alcoholic caustic potash (20%, 50 cc) but gave a neutral gummy product which could not, however, be obtained in a crystalline state.

Pyrolysis of albigenic acid(Ia). Albigenic acid (200 mg) was heated in a metal bath at 250° for 2 min when the evolution of CO_2 subsided. The cold melt in ether furnished an entirely neutral material as an oil which failed to crystallize even after repeated chromatography.

Lactone diacetate of albigenic acid (VII). A solution of albigenic acid (Ia, 300 mg) in glacial acetic acid (10 cc) was treated with hydrobromic acid (48%, 10 cc) and acetic anhydride (3 cc) and the

* We express our sincere thanks to Prof. Carl Djerassi of Wayne University, Michigan, U.S.A., for sending us an authentic sample of methyl echinocystate.

† The m.p. of albigenic acid recorded in the preliminary communication (*loc. cit*) was 233–236°, which however on prolonged drying over P_2O_5 in high vacuo rose to 246–248° (dec).

[12] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* 75, 422 (1953).

mixture kept at room temp for 5 days. The dark red solution was diluted with water, extracted with ether, washed with a saturated solution of sodium carbonate, dried and evaporated. A solution of the residue in benzene (10 cc) was chromatographed over alumina (50 g). Elution of the column with benzene gave a product, (220 mg) which gave no coloration with tetranitromethane, m.p. 281–282°, $[\alpha]_D^{28}$ −24°. The m.p. of this compound when admixed with an authentic sample of 18-iso-echinocystic acid lactone diacetate was undepressed.[12] (Found: C, 73·1; H, 9·4. $C_{34}H_{52}O_6$ requires: C, 73·4; H, 9.4%).

Selenium dioxide oxidation of diacetyl methyl echinocystate (III). To a solution of diacetyl methyl echinocystate (m.p. 199–200°; $[\alpha]_D^{30}$ −16°; 2 g) in glacial acetic acid (50 cc), freshly prepared and resublimed selenium dioxide (200 mg, 0·5 mole) was added and the solution refluxed for 17 hr on a sand-bath. The solution, after filtration of the separated red selenium and on pouring into water, gave solids, which were taken up in ether, washed with alkali, dried and evaporated. The residue in benzene (15 cc) was filtered through a column of alumina (200 g). Elution with petroleum ether–benzene mixture (2 : 1, 200 cc) gave (200 mg) m.p. 199–200°, of unreacted diacetate of methyl echinocystate. Petroleum ether–benzene mixture (1 : 1, 1 l.) eluted a fraction, as a glassy mass which showed no tendency to crystallize even after repeated chromatography. Benzene (500 cc) eluate gave a third fraction (IVa), crystallizing as colourless plates from dilute ethanol, m.p. 236–237°, $[\alpha]_D^{33}$ −134° (500 mg). It gave a yellow colour with tetranitromethane. λ_{max} 244, 252, 260 mμ (log ε 4·40, 4·44, 4·26 respectively). (Found: C, 75·0; H, 9·49. $C_{32}H_{50}O_3$ requires: C, 75·24; H, 9·56%).

Hydrogenation of the diene (IVa) *to* (Id). A solution of the diene (IVa, 400 mg) in glacial acetic acid (50 cc) was shaken with platinum oxide catalyst (300 mg) in an atmosphere of hydrogen at room temp and at atmospheric pressure, till one mole of the gas was consumed. Filtration of the catalyst and evaporation of the filtrate *in vacuo* left a residue, which after purification by chromatography over alumina, crystallized as shining leaflets, (Id, 380 mg) m.p. 205–206°, $[\alpha]_D^{28}$ −6°, and showed no absorption maxima above λ 220 mμ. It gave a pale yellow colouration with tetranitromethane. (Found: C, 74·98; H, 9·82. $C_{32}H_{52}O_3$ requires: C, 74·96; H, 9·91%).

Oxidation of the above compound (Id) to (V). A solution of the compound (Id, 150 mg) in pyridine (5 cc) was added to a suspension of chromium trioxide–pyridine complex prepared from 200 mg of CrO_3 and 5 cc of pyridine at 15°, and the mixture kept for 24 hr. The product after chromatography over alumina, furnished colourless needles (V) from methanol, m.p. 251–253°, $[\alpha]_D^{28}$ −151° which showed no coloration in the Zimmermann test. (Found: C, 75·5, H, 9·48; $C_{32}H_{50}O_3$ requires: C, 75·24; H, 9·56%).

Acetylation of (Id) *to form diacetyl methyl albigenate* (Ic). 200 mg of the compound (Id) was heated over a steam-bath with pyridine (2 cc) and acetic anhydride (3 cc) for 3 hr. The product m.p. 181–188° (180 mg) was adsorbed on a column of alumina (25 g). Elution with benzene–petroleum ether mixture (1 : 1, 150 cc) gave needles crystallizing from dilute ethanol m.p. 189–190°, $[\alpha]_D^{28}$ −53°, which showed no change in m.p. or specific rotation when admixed with a pure sample of diacetyl methyl albigenate (Ic).

Acknowledgements—The authors are greatly indebted to Dr. D. M. Bose, Director and to Dr. P. K. Bose, Head of the Department of Chemistry, Bose Institute, for their keen interest and encouragement in the work. Thanks are due to Mrs. C. Dutta of University College of Science and Technology, Calcutta, for carrying out the microanalysis.

[12] P. Bilham and G. A. R. Kon, *J. Chem. Soc.* 552 (1941).

VOL. 7 1959

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POLY-*ISO*OXAZOLES

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(*Received* 27 *January* 1959)

Abstract—The reaction of hydroximic chlorides on acetylenic Grignard reagents has been applied to the synthesis of unknown *poly*-iso*oxazoles*. Some linear poly-*iso*oxazoles of unequivocal structure, viz. 3:3′:5′:3″-tri-*iso*oxazole (IX), 3:3′:5′:5″-tri-*iso*oxazole (XIV), 3:3′:5′:5″:3″:3‴-tetra-*iso*oxazole (XV) and 3:3′:5′:5″:3″:3‴:5‴:5^{IV}:3^{IV}3^{V}-hexa-*iso*oxazole (XVII) have been prepared.

IN previous papers[1] we have reported the synthesis of three of the six theoretically possible bi-*iso*oxazoles (I) namely 3:3′-(II), 5:5′-(III) and 3:5′-bi-*iso*oxazole (IV).

I

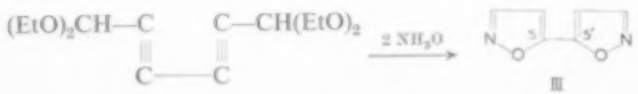
These substances have been prepared by the following reactions:

(a) action of suitable hydroximic chlorides (dichloroglyoxime, 3- and 5-*iso*-oxazolylformohydroximic chloride) on ethynylmagnesium bromide:

II

IV

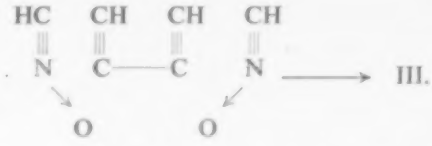
(b) action of hydroxylamine on hexadiindial tetraethylacetal:



III

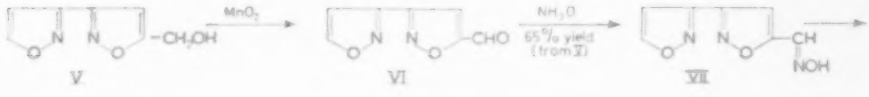
[1] A. Quilico, G. Gaudiano and A. Ricca, *Gazz. Chim. Ital.* **87,** 638 (1957); G. Gaudiano and A. Ricca, *Ibid.* **89,** (1959); A. Ricca and G. Gaudiano, *Reudic. Acc. Naz. Lincei* [VIII], **26,** In press (1959). P. Grünanger and E. Fabbri, *Ibid.* **89,** (1959); A. Quilico, G. Gaudiano and L. Merlini, *Tetrahedron* **2,** 359 (1958).

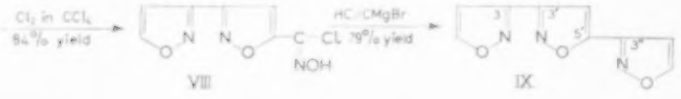
(c) addition of fulminic acid on diacetylene



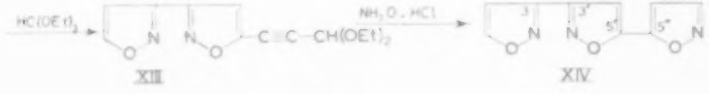
By extending reactions (a) and (b) to hydroximic chlorides and acetylene derivatives containing one or two *iso*oxazole rings we have succeeded in synthesizing linear poly-*iso*oxazoles of unequivocal structure in which three, four and six *iso*oxazole rings are present to form a normal skeleton of respectively nine, twelve and eighteen carbon atoms.

3:3′:5 :3″-*Tri*-iso*oxazole* (IX)* has been synthesized from 5′-hydroxymethyl-3:3′-bi-*iso*oxazole (V)[1] according to the reactions in an overall yield of 43 per cent.





The isomeric 3:3′:5′:5″-*tri*-iso*oxazole* (XIV), was prepared as follows from 3-*iso*oxazolylformohydroximic chloride (X).



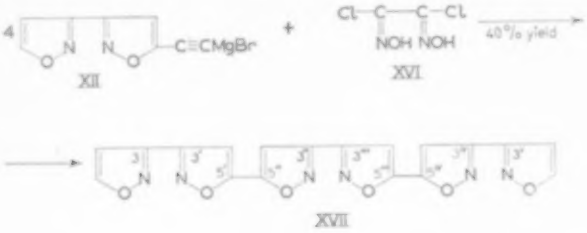
3:3′:5′:5″:3″:3‴-*Tetra*-iso*oxazole* (XV) was obtained by reacting 3-*iso*oxazolyl-formohydroximic chloride (X) with diacetylene organomagnesium bis-derivative:

Since in the preparation of butadiinylmagnesium bromide it is impossible to prevent the formation of the bis-derivative, an appreciable quantity of tetra-*iso*oxazole (XV) is formed in the preparation of ethynyl-bi-*iso*oxazole (XI). In the above reaction

* 3:3′-Dimethyl-5:5′:3′:5″-tri-*iso*oxazole, 5:5″-dimethyl-3:3′:5′:3″-tri-*iso*oxazole and a mixture of the 3:5″-dimethylderivatives of 5:5′:3′:3″- and 5,3′:5′:3″-tri-*iso*oxazole had been reported by Musante, *Gazz. Chim. Ital.* **71**, 172 (1941). They were prepared by treatment of *iso*oxazole β-diketones with hydroxylamine.

owing to the presence of some diacetylene monomagnesium derivative, a certain amount of the hydroximic chloride (X) is converted into ethynyl-bi-*iso*oxazole.

Application of reaction (a) to ethynyl-bi-*iso*oxazole (XI) led to the synthesis of linear 3:3′:5′:5″:3″:3‴:5‴:5^{IV}:3^{IV}:3^{V}-*hexa*-iso*oxazole* (XVII). It was obtained (in 40 per cent yield on the chloroxime) by treating dichloroglyoxime (XVI) with an excess of bi-*iso*oxazolylethynylmagnesium bromide (XII).



The new poly-*iso*oxazoles are crystalline solids which can be sublimed undecomposed *in vacuo*. As expected, their melting points (Table 1) rise with the molecular weight, whereas their solubility in the usual organic solvents rapidly diminishes. They are not fluorescent at the Wood's light.

The *U.V. Spectra* of the new poly-*iso*oxazoles are reported in Fig. 1 in comparison with the bi-*iso*oxazoles already described. As Speroni *et al.* pointed out, 3:3′-bi-*iso*oxazole (λ_{max} = 214 mμ) practically contains the same chromophore as *iso*oxazole

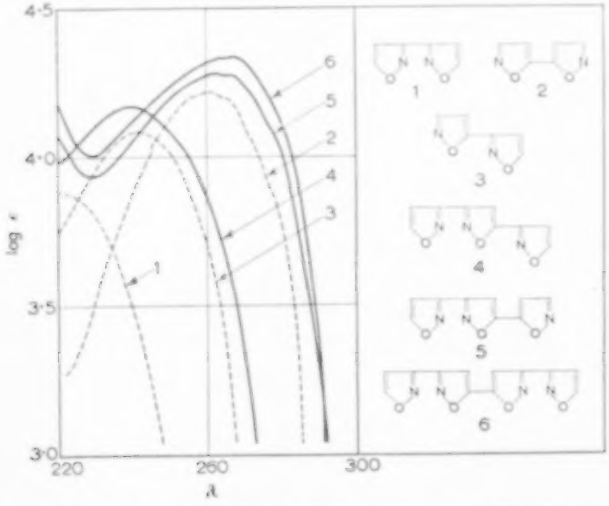


FIG. 1. Ultra-violet spectra of poly-*iso*oxazoles (in ethanol).

itself (λ_{max} = 214 mμ) because the 3:3′-linkage prevents the conjugation of the two *iso*oxazole rings.[2] In 5:5′-bi-*iso*oxazole a strong interaction between the two rings occurs with the appearance of a new chromophore (λ_{max} = 260 mμ). 3:5′-Bi-*iso*oxazole

[2] S. Califano, G. Speroni and D. Tafuri, private communication.

U.V. spectrum exhibit a well defined maximum at 242 in a position which is intermediate between those of 3:3′- and 5:5′-bi-*iso*oxazole maxima.

From the point of view of their spectrochemical behaviour the new poly-*iso*oxazoles can be classified as follows:

(i) Those which contain a 5:5-linkage conjointly with 3:3-linkages (3:3′:5′:5″-tri-*iso*oxazole and 3:3′:5′:5″:3″:3‴-tetra-*iso*oxazole) show a U.V. spectrum similar to

TABLE 1. PHYSICAL PROPERTIES OF POLY-*iso*OXAZOLES

Compound	m.p.	U.V. Spectrum in ethanol	
		λ_{max}, mμ	log ε
3:3′-Bi-*iso*oxazole (II)	73–73·5°	210	3·90
5:5′-Bi-*iso*oxazole (III)	116–117·5°	260	4·21
3:5′-Bi-*iso*oxazole (IV)	86–87°	242	4·08
3:3′:5′:3″-Tri-*iso*oxazole (IX)	153–155°	239	4·175
3:3′:5′:5″-Tri-*iso*oxazole (XIV)	160–161°	263	4·28
3:3′:5′:5″:3″:3‴-Tetra*iso*oxazole (XV)	265°	267	4·335
3:3′:5′:5″:3″:3‴:5‴:5^{IV}:3^{IV}:3^{V}-Hexa-*iso*oxazole (XVII)	370° dec	*	*

* Not determined, being insoluble in ethanol.

that of 5:5′-bi-*iso*oxazole (λ_{max} at about 265 mμ) as well for the position of the maximum as for the presence of a clearly recognizable fine structure.

(ii) Those which contain a 3:5-linkage conjointly with 3:3 linkages (3:3′:5′:3″-tri-*iso*oxazole) show a U.V. spectrum very similar to that of 3:5′-bi-*iso*oxazole with a single maximum at about 240 mμ.

This investigation will be completed by the study of poly-*iso*oxazoles containing 3:5-and 5:5-linkages, whose synthesis is in progress; it can however be anticipated that conclusive information about the structure of poly-*iso*oxazole systems is supplied by the study of U.V. spectra.

The *I.R. spectra* of the new poly-*iso*oxazoles are reported in Fig. 2. Especially characteristic for the constancy of their position and intensity are the bands located at 3·2, 6·5 and 9·0 μ.

Syntheses of octa-*iso*oxazoles and still higher linear poly-*iso*oxazoles are in progress.

EXPERIMENTAL

Oxime of 3:3′-*bi*-iso*oxazole-5′-aldehyde* (VII). Precipitated MnO_2 (55 g) was added to a solution of 5′-hydroxymethyl-3:3′-bi-*iso*oxazole (7·7 g) in acetone (500 ml), and the mixture allowed to stay at room temp for 20 hr. The MnO_2 was then filtered off and washed repeatedly with acetone. The combined filtrate and washings, evaporated under reduced pressure, left a solid residue of 3:3′-bi-*iso*oxazole-5′-aldehyde and unreacted carbinol. The mixture was refluxed for about 15 min with a solution of $NH_2O.HCl$ (6·0 g) and Na_2CO_3 (4·6 g) in water (100 ml); on cooling, crystals of the oxime of (VII) and unchanged carbinol separated.

The reaction mixture was rendered slightly alkaline with N NaOH and the undissolved carbinol (3·4 g) recovered by filtration. The alkaline filtrate on treatment with 10% HCl gave the oxime (1·7 g); from the filtered acid solution a further 1·9 g of carbinol were recovered by extraction with ether. Yield of oxime 65% based on the reacted carbinol.

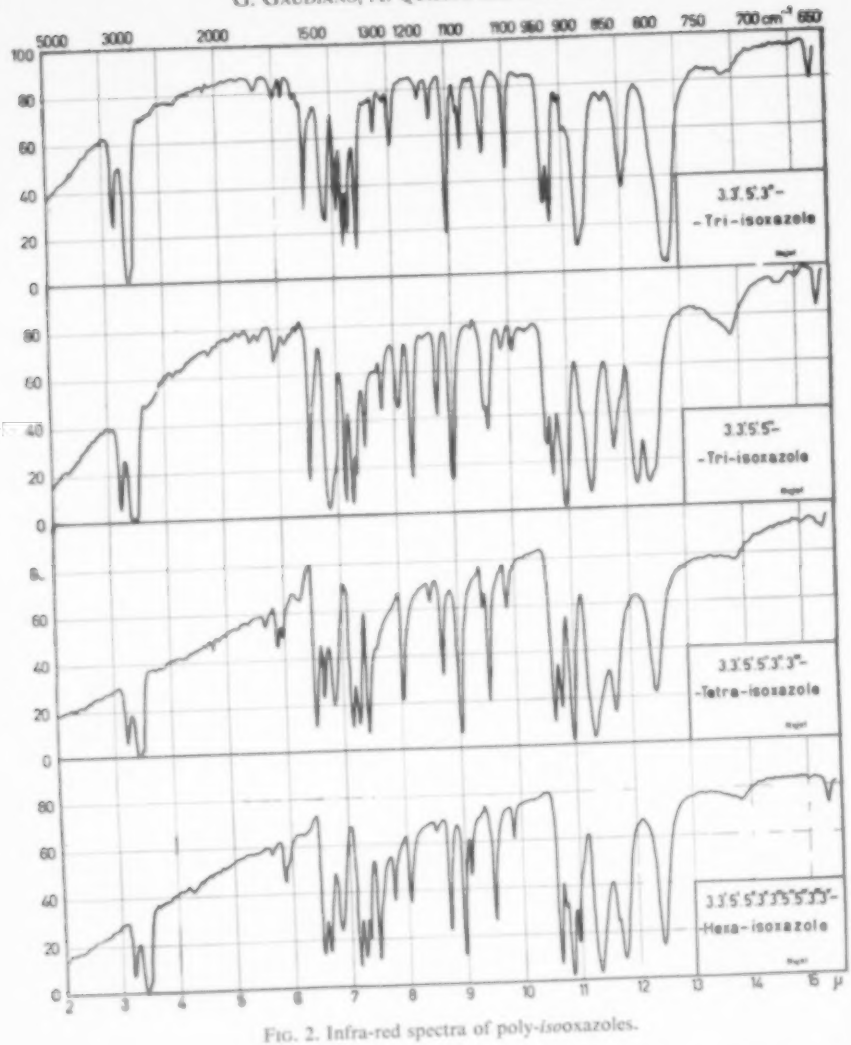


FIG. 2. Infra-red spectra of poly-*iso*oxazoles.

3:3′-Bi-*iso*oxazole-5′-aldoxime crystallizes from hot water in soft white needles m.p. 187–189°. (Found: N, 23·60; $C_7H_5O_3N_3$ requires: N, 23·46%).

3:3′-Bi-iso*oxazolyl*-5′-*formohydroximic chloride* (VIII). A suspension of VII (1·0 g) in dry carbon tetrachloride (20 ml) was cooled with ice and treated for 10 min with a slow stream of chlorine. After remaining overnight at 0–5° the crystallized hydroximic chloride was filtered and washed with dry CCl_4. Yield 1·0 g (84%). The product was purified by sublimation *in vacuo* (at 150–170° under 0·5 mm Hg). Pure hydroximic chloride (VIII) forms a microcrystalline powder m.p. 219–221°. (Found: N, 19·66; $C_7H_4ClO_3N_3$ requires: N, 19·67%).

Synthesis of 3:3′:5′:3″-*tri*-iso*oxazole* (IX). A suspension of VIII (2 g) in tetrahydrofuran (20 ml) was added in small portions, over a period of 15 min with continual stirring and cooling with water, to the solution of ethynylmagnesium bromide in tetrahydrofuran prepared from 0·53 g of magnesium.[3] After 3 hr stirring the reaction mixture was left overnight at room temp, decomposed with ice and HCl, and then extracted with ether. On distilling the ether solution (dried over Na_2SO_4) a solid residue (1·5 g) of crude tri-*iso*oxazole was obtained (79%). Pure tri-*iso*oxazole crystallizes from hot

[3] E. R. H. Jones, K. L. Skattebol and M. C. Whiting, *J. Chem. Soc.* 4765 (1956).

water in small needles m.p. 153–155° and can readily be sublimed at reduced pressure. (Found: N, 20·64; $C_9H_5O_3N_3$ requires: N, 20·69%). U.V. and I.R. spectra are reported in Figs. 1 and 2.

5′-Ethynyl-3:3′-bi-isooxazole (XI). A solution of X[1] (10 g) in tetrahydrofuran (100 ml) was added over a period of 10 min with continual stirring and cooling with ice-water to the suspension of butadiinylmagnesium bromide prepared from 4·0 g of magnesium.[3] During the reaction dissolution of the diacetylene organomagnesium derivative and separation of a fine whitish precipitate were observed. After 6 hr stirring the mixture was left overnight at room temp and then decomposed with ice and HCl. The white powder left undissolved after this treatment (dry 1·8 g) consisted of pure 3:3′:5′:5″:3″:3‴-tetra-*iso*oxazole (XV) (19% yield). The aqueous solution from the filtration of XV was repeatedly extracted with ether. The combined extracts, dried over Na_2SO_4 and decolorized with Norit gave, after removal of the solvent, a solid residue which recrystallized from hexane (about 200 ml) as pure 5′-ethynyl-3:3′-*iso*oxazole (5 g). A further portion (1·3 g) was recovered from the hexane mother liquors. Overall yield was 77%.

Pure ethynyl-bi-*iso*oxazole crystallizes from hexane in white needles m.p. 82–83°. The product is volatile in steam and sublimes easily. (Found: N, 17·31; $C_8H_4O_2N_2$ requires: N, 17·50%).

3:3′-Bi-isooxazolyl-5′-propargylic aldehyde diethylacetal (XIII). A solution of XI (5 g) in dry ether (50 ml) was added in about 30 min with continual stirring to the cooled solution of ethylmagnesium bromide prepared from 0·84 g of magnesium. After additional 30 min stirring 5·1 g of freshly distilled ethyl orthoformate dissolved in 100 ml of dry benzene were added dropwise with constant stirring and cooling. Most of the ether was then removed by distillation and the reaction completed by refluxing on the water bath for 4 hr. The dark coloured reaction mixture obtained was decomposed with ice-water and ammonium acetate (10 g) and then extracted with ether. The organic layer dried over K_2CO_3 left, after removal of the solvent and unreacted ethyl orthoformate *in vacuo*, the crude diethylacetal (XIII) as a brown oil which was used without further purification for the synthesis of 3:3′:5′:5″-tri-*iso*oxazole.

Synthesis of 3:3′:5′:5″-*tri-isooxazole* (XIV). XIII was refluxed for 2½ hr with $NH_2OH.HCl$ (2·5 g) dissolved in aqueous ethanol (30 ml ethanol + 10 ml water). After removing most of the ethanol, at reduced pressure, the reaction mixture was diluted with water and the yellowish precipitate collected on a filter. It weighed when dry 0·4 g. Purified by recrystallization from hot water 3:3′:5′:5″-tri-*iso*oxazole forms soft needles m.p. 160–161°. The product is not volatile in steam and is very soluble in ethanol. (Found: N, 20·76; $C_9H_5O_3N_3$ requires: N, 20·69%). U.V. and I.R. spectra are shown in Figs. 1 and 2.

Synthesis of 3:3′:5′:5″:3″:3‴-*tetra-isooxazole* (XV). A solution of diacetylene (1·7 g) in tetrahydrofuran (15 ml) was added over a period of 5 min to the solution of ethylmagnesium bromide prepared from 1·5 g of magnesium in 80 ml of tetrahydrofuran.[4] During the reaction the mixture was continually stirred and cooled with ice-water. After additional 2½ hr stirring at room temp, a solution of dichloroglyoxime (5 g) in tetrahydrofuran (50 ml) was added dropwise in about 20 min. The mixture was left overnight and then decomposed with ice-water and HCl. The crude tetra-*iso*oxazole was precipitated as a fine powder (2·1 g 46·5%). The product is sparingly soluble in most organic solvents; from boiling ethanol or benzene it crystallizes as microscopic needles m.p. 265° which sublime when heated *in vacuo*. (Found: N, 20·53; $C_{12}H_6O_4N_4$ requires: N, 20·74%). U.V. and I.R. spectra are reported in Figs. 1 and 2.

The acid solution recovered after filtration of the tetra-*iso*oxazole and extracted with ether gave XI (0·8 g 14·7%).

Synthesis of 3:3′:5′:5″:3‴:5⁗:5^{IV}:3^{IV}:3^{V}-*hexaisooxazole* (XVII). A solution of XI (5 g) in tetrahydrofuran (25 ml) was added in 10 min with continual stirring and cooling with water, to the solution of ethylmagnesium bromide prepared as usual from 0·84 g of magnesium in 30 ml of the same solvent. The formation of the ethynyl-bi-*iso*oxazole magnesium derivative was completed by heating on the water-bath at 40° for 20 min.

After cooling the dark coloured clear solution with ice dichloroglyoxime (1·37 g) dissolved in tetrahydrofuran (10 ml) was added in 10 min with continual stirring. A fine precipitate was immediately formed. The reaction mixture was stirred at ordinary temp for 1½ hr, allowed to remain overnight, and then decomposed with ice-water and HCl. The light-brown precipitate of crude hexa-*iso*oxazole was collected on a filter, washed with water, ethanol and ether (dry 1·3 g, 40%). From the aqueous solution unchanged ethynyl-bi-*iso*oxazole (2 g) were recovered by extraction with ether.

[4] J. B. Armitage, E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.* 46 (1951).

VOL. 7 1959

Hexa-*iso*oxazole is practically insoluble in ethanol and in most organic solvents, sparingly soluble in boiling nitrobenzene from which it separates as microscopic shining needles. It is most conveniently purified by sublimation at reduced pressure (250–280° under 0·5 mm Hg). At temp above 300° at ordinary pressure it sublimes unaffected. When heated in a sealed capillary tube it melts at 370° with decomposition. (Found N, 20·82; $C_{18}H_6O_6N_6$ requires: N, 20·79%). For its I.R. spectrum see Fig. 2.

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STUDIES IN THE XANTHONE SERIES—IV*

PREPARATION AND REACTIONS OF 2-ALLYL-1-HYDROXYXANTHONE

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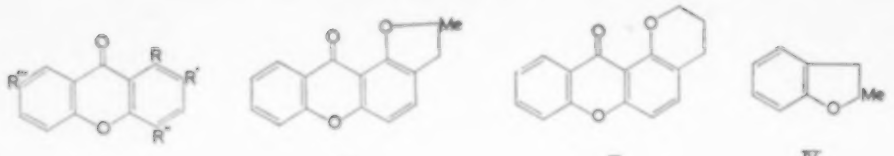
Abstract—Preparations of furano-(II and V) and pyranoxanthones (III) from 2-allyl-1-hydroxyxanthone (I; R = OH, R′ = $CH_2CH{:}CH_2$, R″ = R‴ = H) and the orientation of 2-formyl-1-hydroxyxanthone (I; R = OH, R′ = CHO, R″ = R‴ = H) and of 4-acetyl-1-hydroxyxanthone (I; R = OH, R′ = R‴ = H, R″ = Ac) are described. The ultra-violet absorption spectra of the new ring systems and their intermediates are briefly discussed.

FURTHER reactions of 1-hydroxyxanthones[1] have been investigated with a view to preparing simple analogues of pharmacologically active chromones such as khellin.[2] 2-Allyl-1-hydroxyxanthone (I; R = OH, R′ = $CH_2CH{:}CH_2$, R″ = R‴ = H) was made by a Claisen rearrangement of 1-allyloxyxanthone[3] (I; R = $OCH_2CH{:}CH_2$, R′ = R″ = R‴ = H) effected by heating the ether alone or with an even higher yield by refluxing it in dimethyl aniline. Claisen[4,5] rearranged the allyl ether of phenol with pyridine hydrochloride and obtained some 2-methylcoumaran (IV), but under similar conditions 1-allyloxyxanthone de-etherified.

2-Allyl-1-hydroxyxanthone was made to react with hydrogen bromide under carefully chosen conditions in order to predetermine the direction of addition. Thus 2-β-bromoprpoyl-1-hydroxyxanthone (I; R = OH, R′ = $CH_2CHBrCH_3$, R″ = R‴ = H) was prepared by saturating a solution of 2-allyl-1-hydroxyxanthone in glacial acetic acid kept under nitrogen with hydrogen bromide gas in the presence of a peroxide inhibitor (diphenylamine). Cyclization of this bromo-compound by refluxing in ethanolic sodium ethoxide occurred almost quantitatively and gave a furanoxanthone which must have the structure (II). This product was also obtained, but only in low yield, by refluxing 2-allyl-1-hydroxyxanthone in a mixture of hydrobromic (48%) and acetic acid followed by cyclization of the crude intermediate with sodium ethoxide. Anti-Markownikoff addition with hydrogen bromide was carried out not on the free phenol (I; R = OH, R′ = $CH_2CH{:}CH_2$, R″ = R‴ = H) since the hydroxyl group might have inhibited the free radical reaction, but on 1-acetoxy-2-allylxanthone (I; R = OAc, R′ = $CH_2CH{:}CH_2$, R″ = R‴ = H) in hexane solution in presence of traces of dibenzoyl peroxide. The crude mixture of 2-γ-bromopropyl-1-hydroxyxanthone (I; R = OH, R′ = $CH_2CH_2CH_2Br$, R″ = R‴ = H) and its O-acetyl derivative (I; R = OAc, R′ = $CH_2CH_2CH_2Br$, R″ = R‴ = H) resulting from this reaction was cyclized in high yield to 5′:6′-dihydropyrano(2′:3′-1:2)xanthone (III).

* Part III. F. Lamb and H. Suschitzky, *Tetrahedron* **5**, 1 (1959).

[1] J. S. H. Davies, F. Scheinmann and H. Suschitzky, *J. Chem. Soc.* 2140 (1956).
[2] C. P. Huttrer and E. Dale, *Chem. Rev.* **48**, 543 (1951).
[3] A. Mustafa and Orkede H. Hishmat, *J. Amer. Chem. Soc.* **79**, 2225 (1957).
[4] L. Claisen, *Liebigs Ann.* **418**, 69 (1919).
[5] L. Claisen and E. Tietze, *Liebigs Ann.* **81**, 449 (1926).



I II III IV

Hurd and Hoffman[6] prepared methyl coumaran and chroman derivatives by an analogous route. The hydrogen bromide adducts were, however, not isolated and the endproducts were known beforehand. Their work confirms that, by using the "peroxide effect" the direction of the ring-closure in *o*-allylphenols may be reliably controlled.

Addition of bromine to 2-allyl-1-hydroxyxanthone gave the dibromo-adduct (I; R = OH, R′ = $CH_2CHBrCH_2Br$, R″ = R‴ = H) from which two molecules of hydrogen bromide were eliminated by treatment with ethanolic sodium ethoxide to give a cyclic ether. By analogy with the results of Adams and Rindfusz[7] who cyclized *o*-allylphenols by the same method, we assign the furano-structure (V) to our product although attempts to convert the furanoxanthone (II) by dehydrogenation into V failed.

Other methods of synthesizing extended xanthones were studied: thus condensations of 1-hydroxyxanthone with ethyl acetoacetate under Pechmann and Simonis conditions were unsuccessful. Experiments to cyclize 1-acetonyloxyxanthone (I; R = OCH_2COCH_3, R′ = R″ = R‴ = H) with polyphosphoric,[8] sulphuric,[9] or with hydrobromic acid in glacial acetic acid[10] gave only starting material in the first two cases and 1-hydroxyxanthone in the third case. When it was found that ethyl bromopropionate could not be made to condense with 1-hydroxyxanthone (cf. ethyl bromoacetate condensation[1]) the preparation of extended xanthones by ring-closure of ethers was not further pursued.

Successful formylations of hydroxyxanthones with hexamine in glacial acetic acid have been reported recently; thus 1-formyl-2-hydroxyxanthone[11] (I; R = CHO, R′ = OH, R″ = R‴ = H) was prepared by this method in about 34 per cent yield and 1-hydroxy-7-methoxyxanthone (I; R = OH, R′ = R″ = H, R‴ = OMe) gave a formyl derivative in similar yields.[12] However, formylation of 1-hydroxyxanthone under similar and modified conditions gave mainly starting material and only a small amount of 2-formyl-1-hydroxyxanthone (I; R = OH, R′ = CHO, R″ = R‴ = H). The structure of this aldehyde follows from its analysis and a comparison of its ultraviolet spectrum with the spectra of the 2- and the 4-acetyl-1-hydroxyxanthone (see Fig. 1).

We reported earlier[1] that in the preparation of 2-acetyl-1-hydroxyxanthone (I; R = OH, R′ = Ac, R″ = R‴ = H) a small amount of an unidentified ketone was also isolated. Mustafa and Hishmat[3] repeated our work but were unable to obtain the unidentified substance which we have now shown to be 4-acetyl-1-hydroxyxanthone (I; R = OH, R′ = R‴ = H, R″ = Ac) by the following unambiguous

[6] C. D. Hurd and W. A. Hoffman, *J. Org. Chem.* **5**, 212 (1940).
[7] R. Adams and R. E. Rindfusz, *J. Amer. Chem. Soc.* **41**, 648 (1919).
[8] W. Davies and S. Middleton, *Chem. & Ind.* 599 (1957).
[9] H. Curd and A. Robertson, *J. Chem. Soc.* 714, 1173 (1933).
[10] C. K. Bradsher and W. J. (Jr.) Jackson, *J. Amer. Chem. Soc.* **76**, 734 (1954) and other papers in this series.
[11] J. S. H. Davies, F. Lamb and H. Suschitzky, *J. Chem. Soc.* 1790 (1958).
[12] E. M. Philbin, J. Swirski and T. S. Wheeler, *J. Chem. Soc.* 4455 (1956).

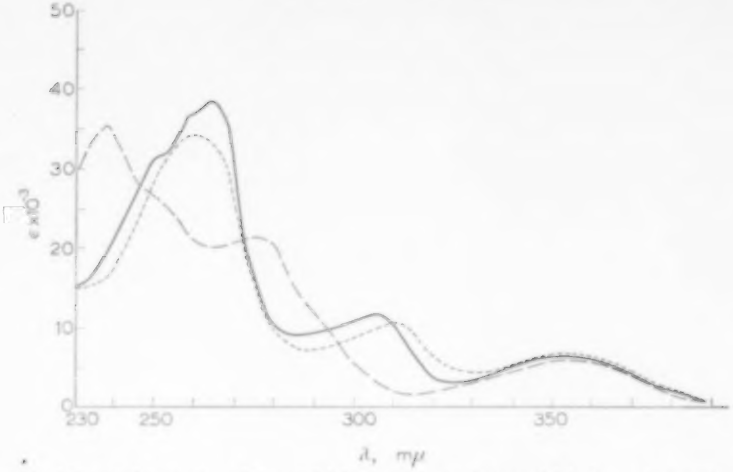
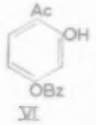


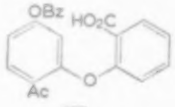
FIG. 1. Ultra-violet spectra of 2-acetyl-1-hydroxy (—); 2 formyl-1-hydroxy (– – – –) and 4-acetyl-1-hydroxyxanthone (— —).

synthesis: *o*-chlorobenzoic acid and 4-benzyloxy-2-hydroxyacetophenone (VI) were condensed under Ullmann conditions and gave the diphenylether (VII) which, by treatment with tetraphosphoric acid, was cyclized and debenzylated in one step yielding 4-acetyl-1-hydroxyxanthone (I; R = H, R′ = R″ = H, R‴ = Ac).

V



VI



VII

A discussion and interpretation of the ultra-violet spectra of xanthones with a conjugated angular ring or with groups in the 1 and 1:2 positions capable of chelation have been given previously.* It will again be noticed from some further examples quoted below (Table 1) that such xanthones show a marked drop in the intensity of the principal absorption band without appreciable shift in the wavelength of the maximal absorption when compared with the spectrum of xanthone. This behaviour is ascribed to steric interference with the planarity of the molecule. The spectrum of 1-hydroxyxanthone has previously been measured by Mull and Nord[13] and is in good agreement with ours, but these authors report a spectrum for 1-methoxyxanthone almost identical with that for 1-hydroxyxanthone. We suspected this result since the marked hypochromic effect in the principal maximum of 1-hydroxyxanthone (Table 1) is undoubtably due to chelation and should disappear when hydrogen bonding is prevented (cf. 1-acetoxyxanthone, Table 1). We, therefore, measured the spectrum of 1-methoxy-xanthone and observed the expected intensity increase relative to 1-hydroxyxanthone.

EXPERIMENTAL

Ultra-violet spectra were measured in methanol on a Unicam S.P. 500 spectrophotometer, except the spectrum of γ-pyrono(2′:3′-1:2)xanthone-6′-carboxylic acid, which was determined in peroxide free dioxan. The spectra are quoted as λ_{max} (mμ) with ε in parentheses.

* See footnote on p. 31.

[13] R. P. Mull and F. F. Nord, *Arch. Biochem.* **4**, 419 (1944).

1-*Allyloxyxanthone* (I; R = $OCH_2CH{:}CH_2$, R′ = R″ = R‴ = H)

A mixture of 1-hydroxyxanthone (8·48 g), allyl chloride (6·0 g), sodium iodide (12·0 g) and potassium carbonate (16·6 g) in dry acetone (350 cc) was boiled under reflux (ca. 30 hr) until a test sample did not give the characteristic ferric chloride colouration of 1-hydroxyxanthone. The inorganic residue was filtered off, the solvent removed from the filtrate and the residual, white solid (10·1 g) gave on recrystallization (petroleum ether b.p. 60–80°) 1-allyloxyxanthone as fine, white needles, m.p. 86° (Mustafa and Hishmat[5] give m.p. 86–87°) (Found: C, 76·2; H, 4·9. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8%).

When the etherification was carried out with allyl bromide instead of allyl chloride and sodium iodide the yields of allyl ether were lower (cf. Mustafa and Hishmat, *loc. cit.*).

Claisen rearrangement of 1-*allyloxyxanthone*

(a) *By heating alone.* 1-Allyloxyxanthone (2·5 g) was heated at 195–200° (2·5 hr). On recrystallization of the product from aqueous methanol 2-*allyl*-1-*hydroxyxanthone* (I; R = OH, R′ = CH_2CH:

TABLE 1.—PRINCIPAL ABSORPTION MAXIMA OF XANTHONES AND RELATED COMPOUNDS IN METHANOL

Compound	λ_{max}(mμ)	ε_{max}
Xanthone	238	44,200
1-Acetoxyxanthone	238	44,100
1-Methoxyxanthone	236	40,300
Xanthones with conjugated angular rings or chelating groups		
1-Hydroxyxanthone	230	30,600
4-Acetyl-1-hydroxyxanthone	238	35,500
2-Formyl-1-hydroxyxanthone	260	34,400
4-Acetoxyfurano(2′:3′-1:2)xanthone[1]	262	31,000
γ-Pyrono(2′:3′-1:2)xanthone-6′-carboxylic acid[1] ..	226	19,900
Xanthones with non-conjugated angular ring systems		
4′:5′-Dihydro-4′-oxofurano(2′:3′-1:2)xanthone ..	255	38,200
4′:5′-Dihydro-5′-methylfurano(2′:3′-1:2)xanthone ..	254	39,600

CH_2, R″ = R‴ = H) (1·83 g; 73%) was obtained as fine, yellow needles, m.p. 105° (Found: C, 75·8; H, 4·8. $C_{16}H_{12}O_3$ requires: C, 76·2; H, 4·8%). It decolourizes bromine in carbon tetrachloride, gives a green ferric reaction and forms an insoluble sodium salt. It also gives a positive reaction with 2:6-dichlorobenzoquinone chloroimide (Gibbs Reagent) which indicates that the position *para* to the hydroxyl group is unsubstituted.[14]

(b) *By heating in dimethylaniline.* 1-Allyloxyxanthone (1 g) in dimethylaniline (7 cc) was heated under reflux for 3 hr. Acidification with aqueous hydrochloric acid (2 N) precipitated 2-allyl-1-hydroxyxanthone in theoretical yield. Recrystallization from aqueous methanol gave yellow needles, m.p. 104–105°, undepressed on admixture with a sample obtained from method (a).

(c) *By heating with pyridine hydrochloride.* A mixture of 1-allyloxyxanthone (1 g) and dry pyridine hydrochloride (3·5 g) was heated at 200–205° for 2 hr. The product was triturated with water and the residue (0·8 g) m.p. 140–143°, was shown to be impure 1-hydroxyxanthone.

1-*Acetoxy*-2-*allylxanthone*

This was obtained as vitreous cubes, m.p. 107–109° from boiling acetic anhydride containing 1 drop of syrupy phosphoric acid and recrystallized from petroleum ether (b.p. 40–60°) (Found: C, 73·5; H, 5·0. $C_{18}H_{14}O_4$ requires: C, 73·5; H, 4·8%).

[14] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 563 (1957).

VOL. 7 1959

4′:5′-Dihydro-5′-methylfurano(2′:3′-1:2)xanthone (II)

(a) A solution of 2-allyl-1-hydroxyxanthone (8 g) in glacial acetic acid (300 cc) was kept under nitrogen and saturated with hydrogen bromide gas (prepared by the bromine–tetralin method) in the presence of traces of diphenylamine. When the reaction mixture was set aside in the dark at room temp for 5 days 2-*β*-bromopropyl-1-hydroxyxanthone (6·7 g, 63%) m.p. 145–148° separated from the solution and was used in the subsequent cyclization experiment without further purification. The bromocompound crystallizes from aqueous acetic acid or from ethanol as plates or needles, m.p. 148–151°, and gives an intense green colour with aqueous ferric chloride (Found: C, 57·2; H, 4·4; Br, 23·6. $C_{16}H_{13}O_3Br$ requires: C, 57·7; H, 4·0, Br 24·0%). 2-*β*-bromopropyl-1-hydroxyxanthone (6·7 g) was cyclized by refluxing in ethanolic sodium ethoxide (1 g of sodium in 450 cc of ethanol) for 2 hr. Most of the solvent was removed and addition of water (1 l.) precipitated a pale-yellow solid (4·5 g, 90%), which on recrystallization (petroleum ether, b.p. 100–120°) gave *4′:5′-dihydro-5′-methylfurano-(2′:3′-1:2)xanthone*, m.p. 181°, λ_{max} 234 (31,300), 254 (39,600), 364 (7,200) (Found: C, 76·1; H, 4·7. $C_{16}H_{12}O_3$ requires: C, 76·2; H, 4·8%).

(b) A mixture of 2-allyl-1-hydroxyxanthone (0·75 g) bromine-free aqueous hydrobromic acid (48%, 15 cc) and glacial acetic acid (5 cc) was boiled under reflux for 0·75 hr. The crude material obtained by pouring the reaction mixture into ice water was boiled in ethanolic sodium ethoxide ((0·4 g of sodium in 100 cc of ethanol) for 1 hr and then most of the solvent was removed. Addition of water precipitated a residue from which 4′:5′-dihydro-5′-methylfurano(2′:3′-1:2)xanthone (0·15 g, 20%) was extracted with hot benzene.

5′:6′-Dihydropyrano(2′:3′-1:2)xanthone (III)

1-Acetoxy-2-allylxanthone (5 g) in *n*-hexane (550 cc) was saturated with hydrogen bromide gas in the presence of dibenzoyl peroxide (0·15 g) and the reaction mixture allowed to stand in sunlight for 3 days. The yellow solid (2·47 g) which had separated was combined with the residue obtained by evaporation of the mother-liquor. The combined fractions on recyrstallization from aqueous methanol furnished *2-γ-bromopropyl-1-hydroxyxanthone* as yellow needles, m.p. 125–126°, which gives a green ferric reaction (Found: C, 57·5; H, 4·1. $C_{16}H_{13}O_3Br$ requires: C, 57·7; H, 4·0%). Dilution of the aqueous methanolic filtrate with water precipitated a white solid which on repeated recrystallization from petroleum ether (b.p. 60–80°) gave *1-acetoxy-2-γ-bromopropylxanthone* as white needles, m.p. 116° (Found: C, 57·3; H, 4·2. $C_{18}H_{15}O_4Br$ requires: C, 57·6; H, 4·0%). A crude mixture of these products (5 g) was kept under reflux with sodium ethoxide (from 1 g of sodium) in ethanol (450 cc) for 1 hr. Most of the solvent was driven off and the solution was then poured into water (2·5 l.) yielding *5′:6′-dihydropyrano(2′:3′-1:2)xanthone* as fine, white needles, m.p. 166° (4·1 g, 85·5%), depressed on admixture with the isomeric 4′:5′-dihydro-5′-methylfurano-(2′:3′-1:2) xanthone (Found: C, 75·8; H, 4·8. $C_{16}H_{12}O_3$ requires: C, 76·2, H, 4·8%).

1-Acetonyloxyxanthone

Chloroacetone (3·62 g) was added to a stirred mixture of 1-hydroxyxanthone (6·37 g) and anhydrous potassium carbonate (12 g) in dry acetone (300 cc) and the reaction mixture boiled under reflux (9 hr). The yellow precipitate was collected and shown to be the sodium salt of 1-hydroxyxanthone (1·75 g). Removal of the solvent from the filtrate gave a residue which was extracted with chloroform. From the chloroform solution *1-acetonyloxyxanthone* was obtained as fine, white needles, m.p. 172–173° (Found: C, 71·7; H, 4·7. $C_{16}H_{12}O_4$ requires: C, 71·6; H, 4·5%).

Attempts to ring close 1-acetonyloxyxanthone (concentrated sulphuric or polyphosphoric acid) yielded starting material. Cyclization attempts by refluxing with aqueous hydrobromic (48%) and glacial acetic acid for 16 hr led to de-etherification.

2-Formyl-1-hydroxyxanthone (I; R = OH, R′ = CHO, R″ = R‴ = H)

A mixture of 1-hydroxyxanthone (1 g), hexamine (3 g) and glacial acetic acid (10 cc) was heated on a steam-bath (6 hr). Hydrochloric acid (18%, 10 cc) was now added and the heating continued for a further 0·5 hr. Dilution of the reaction mixture with water furnished a yellow precipitate (0·9 g) from which prolonged steam distillation removed 1-hydroxyxanthone (0·6 g) and left a residue which was repeatedly extracted with hot ethanol (10 cc portions). One extract, m.p. ca 170°, gave on repeated recrystallizations (ethanol and petroleum ether, b.p. 100–120°) *2-formyl-1-hydroxyxanthone* (0·02 g), as yellow needles, m.p. 186°, λ_{max} 260 (34,400), 310 (10,600), 355 (7,200) (Found: C, 69·8;

H, 3·3. $C_{14}H_8O_4$ requires: C, 70·0; H, 3·3%). It gives an orange, crystalline 2:4-dinitrophenylhydrazone, and a deep-red ferric reaction.

A by-product from the purification of 2-formyl-1-hydroxyxanthone gave a red gelatinous precipitate with Brady's reagent which suggests the presence of another formyl derivative. When the Duff reaction was carried out in glyceroboric acid or in a mixture of dimethyl formamide and acetic acid, or with more hexamine, the yields of formyl derivative were not improved. With 1-methoxyxanthone no reaction occurred but using 1-acetoxyxanthone the results were as for 1-hydroxyxanthone.

4-Acetyl-1-hydroxyxanthone (I; R = OH, R′ = R‴ = H, R″ = Ac)

4-Benzyloxy-2-hydroxyacetophenone (VI, 8·9 g) and *o*-chlorobenzoic acid (5·2 g) were refluxed in amyl alcohol (40 cc) in the presence of cuprous iodide (0·1 g), copper–bronze (0·1 g) and anhydrous potassium carbonate (9 g). The amyl alcohol-water azeotrope was distilled off and more amyl alcohol (30 cc) was added and the reaction mixture boiled under reflux for 3 hr. Finally the amyl alcohol was removed by steam distillation and the solid residue (which was 4-benzyloxy-2-hydroxyacetophenone, 6·7 g) collected. The filtrate when acidified to pH 2 yielded a gum which on trituration with ethanol gave *2-acetyl-2′-carboxy-5-benzyloxydiphenyl ether* (0·32 g) as fine, white needles, m.p. 152–154° (aqueous ethanol) (Found: C, 72·5; H, 4·9. $C_{22}H_{18}O_5$ requires: C, 72·9; H, 5·0). The ether (0·1 g) and tetraphosphoric acid (3 cc) were heated on a water-bath at 84° for 0·8 hr and the reaction mixture then poured onto crushed ice. The yellow precipitate (0·08 g) when recrystallized twice from aqueous ethanol yielded *4-acetyl-1-hydroxyxanthone*, m.p. 200°, identical with the unidentified substance isolated previously from Friedel–Crafts and Fries reactions on 1-hydroxyxanthone,[1] λ_{max} 238 (35,500), 248 (27,000), 276 (21,300), 358 (6200) (Found: C, 70·9; H, 4·0. $C_{15}H_{10}O_4$ requires: C, 70·9; H, 4·0%). Its 2:4-*dinitrophenylhydrazone* crystallized as orange needles, m.p. 273° (Found: N, 12·7. $C_{21}H_{14}O_7N_4$ requires: N, 12·9%).

Acknowledgements—We wish to thank the Governors of the Royal Technical College, Salford, for a Research Demonstratorship to one of us (F. S.) and are grateful to Mr. P. Naylor, B.Sc., for a gift of a sample of 4-benzyloxy-2-hydroxyacetophenone.

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VOL. 7 1959

TERPENOIDS—XXXIX.[1] IRESIN (PART 5)[2]

COMPLETE STRUCTURE AND ABSOLUTE CONFIGURATION[3,4]

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(*Received* 18 *February* 1959)

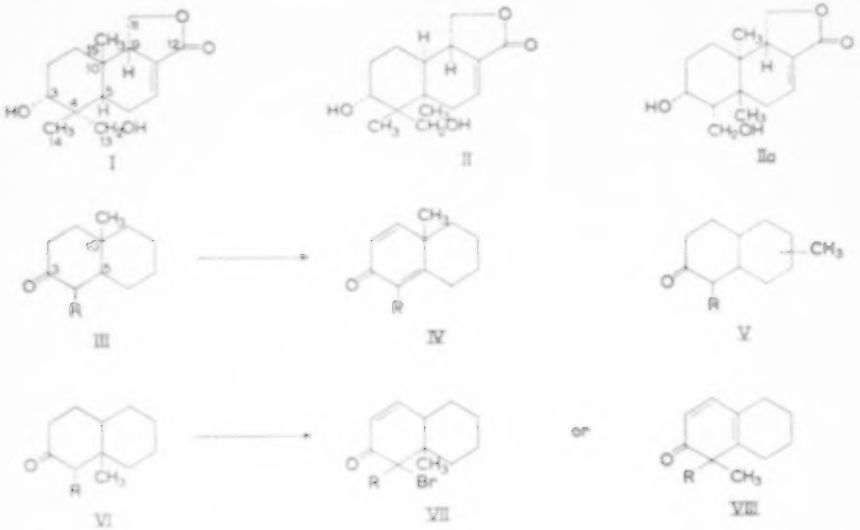
Abstract—The remaining uncertainty in the structure of iresin (I)—the location of the angular methyl group—has now been settled rigorously by comparing the course of tribromination–dehydrobromination experiments of its derived nor-ketone XI with steroid models. Thus it was shown that di- or tri-bromination of 4α-methyldihydrotestosterone acetate leads to 2α,6β-dibromo-4-methyltestosterone acetate, also obtainable by dibromination of 4-methyltestosterone acetate. Rotatory dispersion studies of relevant iresin and steroid model compounds demonstrate that this sesquiterpene possesses the "wrong" absolute configuration as compared to the steroids and higher terpenes.

EARLIER degradation experiments[5] from our Laboratory have shown that the sesquiterpene iresin[6] possesses structure I or II (without the absolute stereochemical implication). We should now like to report experiments[7] which establish expression I for iresin and also settle all outstanding stereochemical details.

The location of an angular methyl group in a polycyclic terpene is usually beset with considerable experimental difficulties[8] and we decided to examine a novel approach involving bromination–dehydrobromination of appropriate ketonic transformation products. The experience gained in this connection has subsequently proved also very useful in locating the angular methyl group of the diterpene cafestol.[9] In principle, the problem resolves itself to differentiating between a bicyclic (or polycyclic) ketone possessing the structural feature found in III, V or VI. Using procedures which have been studied extensively in the steroid series,[10] dibromination *cum* dehydrobromination of ketone III should lead to the cross-conjugated dienone IV, while if the angular methyl group is located at the alternate bridgehead position (VI), a mono-unsaturated ketone (e.g. VII) or a rearranged,[11] linearly conjugated dienone (VIII) should result. If the methyl group is not situated in an angular

[1] Paper XXXVIII; C. Djerassi, R. Mauli and L. H. Zalkow, *J. Amer. Chem. Soc.* **81**, in press (1959).
[2] Part 4; P. Crabbé, S. Burstein and C. Djerassi, *Bull. Soc. Chim. Belg.* **67**, 632 (1958).
[3] Supported by the Division of Research Grants (grant No. RG-3863) of the National Institutes of Health, U. S. Public Health Service.
[4] Taken from Part II of the Ph.D. thesis of Sumner Burstein.
[5] [a] C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan and J. Herran, *J. Amer. Chem. Soc.* **76**, 6410 (1954); [b] C. Djerassi and W. Rittel, *Ibid.* **79**, 3528 (1957).
[6] C. Djerassi, P. Sengupta, J. Herran and F. Walls, *J. Amer. Chem. Soc.* **76**, 2966 (1954).
[7] A preliminary communication outlining these results has already appeared [C. Djerassi and S. Burstein, *J. Amer. Chem. Soc.* **80**, 2593 (1958)] as well as independent confirmation of the structure and relative configuration by X-ray analysis [M. G. Rossmann and W. N. Lipscomb, *Ibid.* **80**, 2592 (1958); *Tetrahedron* **4**, 274 (1958).
[8] Many pertinent examples can be found in J. L. Simonsen and D. H. R. Barton, *The Terpenes* Vol. III. Cambridge University Press (1952).
[9] C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **81**, 2386 (1959).
[10] L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene* (3rd Ed.). Reinhold, New York (1949); C. W. Shoppee, *Chemistry of the Steroids*. Academic Press, New York (1958).
[11] J. M. Beaton, F. S. Spring, R. Stevenson and J. L. Stewart, *Tetrahedron* **2**, 246 (1958).

position (e.g. V), then a phenol would be formed and all of these alternate products could be differentiated by chemical or spectroscopic means.



Since the double bond of iresin (I) would have interfered in the projected bromination experiments, it was decided to operate in the iso-dihydro series[12] and several approaches were examined for the preparation of the required key intermediate, 13-nor-3-dehydroisodihydroiresin (XI). The first method involved acid-promoted cleavage of 3-dehydroisodihydroiresin 13-trityl ether (X),[12] which was accompanied by retroaldolization and provided the desired nor-ketone XI, together with formaldehyde and triphenylcarbinol. Alternatively, the unsaturated 13-nor-ketone XIII, which had been obtained darlier[5b,13] from iresin (I), was hydrogenated to 13-nor-3-dehydrodihydroiresin (XIV)[14] and then subjected to alkaline isomerization leading again to XI.

Since neither method proceeded in satisfactory overall yield, attention was directed towards the direct oxidation[15] of isodihydroiresin (IX) with chromium trioxide in sulfuric acid–acetone.[16] Under suitable conditions, IX could be converted in 64 per cent yield into the keto aldehyde XII, which underwent a reverse Claisen condensation upon treatment with acid (or less satisfactorily with base[17]) to yield the required nor-ketone XI. It is pertinent to note that the keto aldehyde XII did not give a color

[12] The initial hydrogenation product, dihydroiresin (XXVII) can be isomerized wtih base[6] to the stable isodihydroiresin (IX).

[13] C. Djerassi, F. W. Donovan, S. Burstein and R. Mauli, *J. Amer. Chem. Soc.* **80,** 1972 (1958).

[14] This substance has already been obtained in pure form by acid-catalyzed retroaldolization[3] of naturally occurring dihydroiresone (XXVI), but since the latter is extremely rare[3] it could not be employed as starting material in the present investigation.

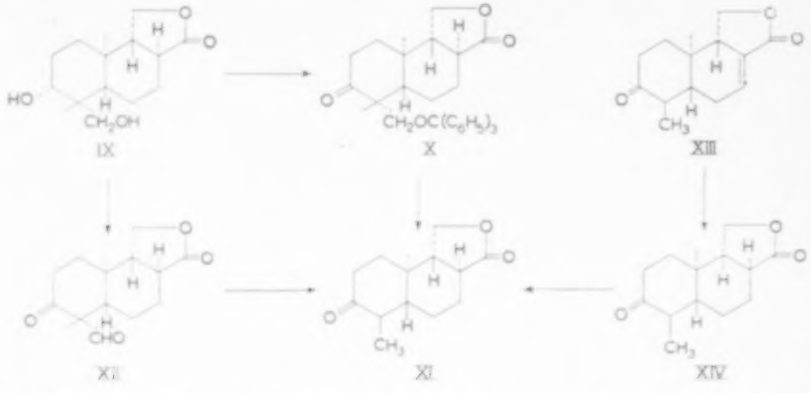
[15] Oxidation with chromium trioxide in pyridine solution does not afford[16] the keto aldehyde XII.

[16] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946). For further references to this oxidation procedure see C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.* **21,** 1547 (1956).

[17] The comparative stability (see experimental) of the keto aldehyde XII towards base is remarkable in view of the known lability [see A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.* **68,** 1715 (1946)] of such formyl ketones and may possibly be ascribed to prior opening of the lactone ring.

with ferric chloride, thus excluding a structure[18] such as IIa from consideration as a possible representation for iresin.

Monobromination of XI led to 2-bromo-13-nor-3-dehydroisodihydroiresin (XV).[19] Ultraviolet[20] and infrared[21] spectroscopic examination confirmed the equatorial orientation of the bromine atom, which represented strong indication[22,23] that the



angular methyl group of iresin was located at C-10 (I). If the nor-ketone XI were actually derived from formulation II (angular methyl group at C-5) of iresin, then the bromine atom would have been expected[22,24] to exhibit an axial orientation.

In order to provide more conclusive evidence bearing on this point, the nor-ketone XI was treated with two molar equivalents of bromine in the expectation that a 2,4-dibromo ketone (XVIII) would be formed,[25] which could then be subjected to dehydrobromination. The presence of two bromine atoms in the crystalline reaction product was demonstrated by analysis, but ultraviolet and infrared spectral examination as well as determination of the optical rotatory dispersion curve (see Fig. 1) clearly showed the presence of an α,β-unsaturated carbonyl moiety. The formation of a double bond implied *in situ* dehydrobromination which in turn required three molar equivalents of bromine. That the reaction had indeed proceeded by a process of disproportionation and had involved three equivalents of bromine was shown by the isolation of the identical product in the tribromination of the nor-ketone XI. The ultraviolet absorption maximum at 262–264 mμ (log ε 4·09) was suggestive of a 2,6-dibromo-Δ^4-3-keto chromophore, since such steroids with an axial 6-bromine

[18] Footnote 23 in ref. 5*b*.

[19] The position of the bromine atom was not established rigorously, but since the A/B *trans* juncture of XI has been proved (*vide infra*), substitution at C-2 follows almost certainly by analogy to the known steric course of the monobromination of *trans*-9-methyl-3-decalones [B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, *J. Amer. Chem. Soc.* **76**, 312 (1954); M. Yanagita and K. Yamakawa, *J. Org. Chem.* **21**, 500 (1956); C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958)].

[20] R. C. Cookson, *J. Chem. Soc.* 282 (1954).

[21] R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **14**, 2828 (1952); R. N. Jones, *Ibid.* **75**, 4839 (1953).

[22] E. J. Corey, *J. Amer. Chem. Soc.* **75**, 2301 (1953) and later papers.

[23] A similar argument has been employed [C. Djerassi, M. Cais and L. A. Mitscher, *J. Amer. Chem. Soc.* **80**, 247 (1958)] in the structure proof of cafestol.

[24] E. J. Corey and J. J. Ursprung, *J. Amer. Chem. Soc.* **78**, 5041 (1956).

[25] Under somewhat different experimental conditions, M. Yanagita and A. Tahara, *J. Org. Chem.* **20**, 959 (1955), isolated such 2,4-dibromo ketones in the tetrahydrosantonin series.

atom absorb near 250 mμ[26] and the additional methyl substituent can be expected to produce a bathochromic shift of at least 10 mμ.[10,27] The correctness of structure XVI as the di- or tri-bromination product of 13-nor-3-dehydroisodihydroiresin (XI) was established by the course of the dehydrobromination with collidine–dimethylformamide which led to a crystalline product to which we are assigning the 1,4,6-trienone formulation XVII. This is consistent with the analytical figures and especially with the ultraviolet absorption spectrum, which exhibited maxima at 224 and 296 mμ

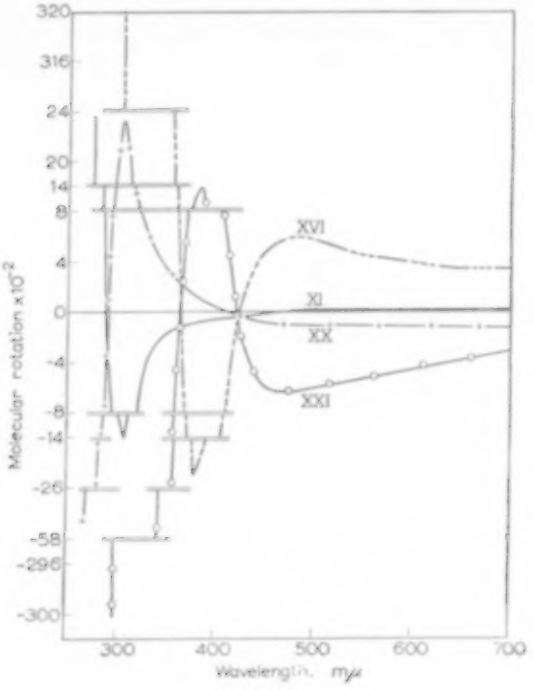


Fig. 1.

and a shoulder at 250 mμ. Steroidal 1,4,6-trien-3-ones (XIX) absorb at 222, 256 and 298 mμ[26a,28] and furthermore, they show three infrared bands in the double bond region between 6·0 and 6·25 μ, which were also noted in the trienone XVII of the iresin series.

Even more striking support for structures XVI and XVII could be presented by model experiments in the steroid series. For this purpose, 4α-methyldihydrotestosterone acetate (XX)[29] was tribrominated under the same conditions employed above for XI, whereupon 2α,6β-dibromo-4α-methyltestosterone acetate (XXI) was obtained in about 50 per cent yield. The axial (β)-orientation of the bromine atom at C-6

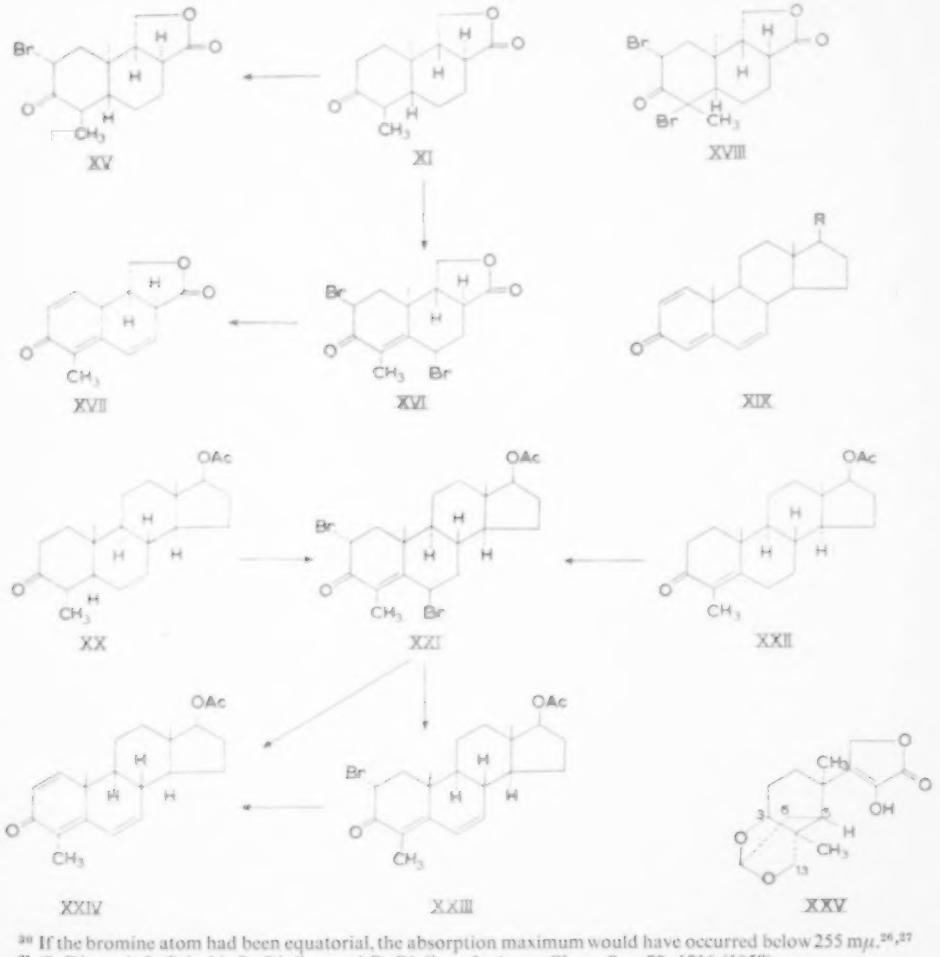
[26] [c] C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, *J. Amer. Chem. Soc.* **72,** 4534 (1950); [b] A. L. Nussbaum, O. Mancera, R. Daniels, G. Rosenkranz and C. Djerassi, *Ibid.* **73,** 3263, footnote 9 (1951); [c] M. Fieser, M. A. Romero and L. F. Fieser, *Ibid.* **77,** 3305 (1955); [d] B. Ellis and V. Petrow, *J. Chem. Soc.* 1179 (1956).

[27] R. B. Woodward, *J. Amer. Chem. Soc.* **64,** 76 (1942).

[28] S. Kaufmann, J. Pataki, G. Rosenkranz, J. Romo and C. Djerassi, *J. Amer. Chem. Soc.* **72,** 4531 (1950).

[29] Y. Mazur and F. Sondheimer, private communication. The synthesis was patterned after that reported for 4α-methylcholestan-3-one [Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.* **80,** 5220 (1958)].

follows from the position of the ultraviolet absorption maximum (263·5 mμ)[30] and from the fact that its rotatory dispersion curve (Fig. 1) was very similar to that[31] of 6β-bromotestosterone acetate and quite distinct from that[31] of the equatorial 6α-isomer. The direct formation of 4-methyl-2,6-dibromo-Δ^4-3-ketones (XVI, XXI) by tribromination of 4-methyl-3-ketones (XI, XX) with the A/B *trans* juncture is best interpreted by assuming initial production of a 2,4-dibromo intermediate (e.g. XVIII) —typical of A/B *trans* 3-keto steroids[10]—followed by spontaneous dehydrobromination to a 2-bromo-Δ^4-3-ketone and allylic bromination[26a] at C-6. The substantial correctness of this assumption was indicated by formation, in good yield, of the identical 2α,6β-dibromo-4-methyltestosterone acetate (XXI) by dibromination in ether–acetic acid solution of 4-methyltestosterone acetate (XXII).[32] These are precisely the conditions under which testosterone acetate yields 2α,6β-dibromotestosterone acetate.[26a]



[30] If the bromine atom had been equatorial, the absorption maximum would have occurred below 255 mμ.[26,27]
[31] C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **80**, 1216 (1958).
[32] F. Sondheimer and Y. Mazur, *J. Amer. Chem. Soc.* **79**, 2906 (1957). We are indebted to Syntex, S. A., Mexico City, for a generous gift of testosterone required in the synthesis of XXII.

Dehydrobromination of 2α,6β-dibromo-4-methyltestosterone acetate (XXI) with collidine–dimethyl formamide proceeded unsatisfactorily and the only pure product which was isolated represented partially dehydrobrominated material in the form of 2-bromo-4-methyl-6-dehydrotestosterone acetate (XXIII), which exhibited a single ultraviolet absorption maximum at the expected position (294 mμ). However, when the dehydrobromination was conducted with lithium carbonate and lithium bromide in dimethyl formamide,[33] there was isolated a difficultly separable mixture of the crystalline 2-bromo-$\Delta^{4,6}$-3-ketone (XXIII) and of oily 4-methyl-$\Delta^{1,4,6}$-androstatrien-17β-ol-3-one acetate (XXIV). The latter was also obtained when the 2-bromo-$\Delta^{4,6}$-ketone XXIII was refluxed for 4 hr with collidine and it did exhibit the characteristic triple ultraviolet absorption maxima[34] at 226, 255 (shoulder) and 306 mμ. Furthermore, its crystalline 2,4-dinitrophenylhydrazone had the expected ultraviolet absorption maximum at 412 mμ.

The above reactions leave no doubt about the correctness of structures XVI and XVII for the transformation products of iresin and these, in turn, are only possible if the sesquiterpene possesses structure I. The alternate expression II does not permit formation of a double bond between positions 4 and 5.

With the structural situation settled, it is now possible to examine in detail the relative and absolute stereochemistry of the molecule. The bromination experiments strongly favor a *trans* ring juncture and this is supported by the rotatory dispersion results discussed below. Using the absolute representation I, a *trans* fusion automatically defines the stereochemistry at C-3 and C-4, since it has already been pointed out earlier[35] that the internal acetal XXV, produced[5b] by ozonolysis of iresin (I), requires that the C-3 hydroxyl group, the 5-6 bond and the C-13 substituent all must be on the same side of ring A. Evidence for the equatorial nature of the C-3 hydroxyl group[36] of iresin has been presented earlier[2,13]—*viz* the formation[2] of dihydroiresin (XXVII) in the sodium borohydride reduction of dihydroiresone (XXVI)—thus defining the relative configuration of four out of the five asymmetric centers of iresin (I).

There remains only the stereochemistry of C-9 and this can be established by considering the course of the catalytic hydrogenation of iresin (I) and its naturally occurring[2] double bond isomer, isoiresin (XXVIII). It has already been noted[12] that the initial product of the catalytic hydrogenation of iresin (I) is dihydroiresin and by assuming entrance of hydrogen from the side opposite to the C-10 angular methyl group, we arrive at stereo-formula XXVII for dihydroiresin. Any remaining doubt is dissipated by the course of the catalytic hydrogenation of isoiresin (XXVIII) which also yielded[2] dihydroiresin (XXVII)[37] and it is inconceivable that in this case adsorption on the catalyst surface and hence entry of hydrogen occurred from the same side of the molecule as the angular methyl group. Dihydroiresin upon treatment with

[33] R. Joly and J. Warnant, *Bull. Soc. Chim. Fr.* 367 (1958).

[34] These values are almost identical with those observed[9] with 4-ethyl-$\Delta^{1,4,6}$-cholestatrien-3-one, which also was noncrystalline, but differ slightly from those observed with the trienone XVII of the iresin series. This slight hyposchromic shift may be due to the lactone ring.

[35] Footnote 26 in ref. 5*b*.

[36] In the internal acetal XXV, this hydroxyl group must, of course, be axial in order to permit construction of a six-membered ring through *meta* substituents of a cyclohexane ring. This requirement is easily accommodated by "flipping" of the ring from one chair conformation into the alternate one, a conformational change which is possible only after ring B has been opened in the ozonolysis of I.

[37] This experiment was actually conducted on the corresponding diacetates.

base at room temperature is isomerized[6] irreversibly in excellent yield to isodihydroiresin. Since it has been shown[5b] that this isomerization involves only inversion of configuration at C-8, then if one accepts expression XXVII for dihydroiresin, IX follows automatically for isodihydroiresin. Inspection of these structures immediately offers a rationalization for the driving force in this isomerization, since in the unstable dihydroiresin (XXVII), the carboxyl group of the lactone is axially oriented. In the stable isomer, isodihydroiresin (IX), this is now equatorial thus relieving the strong 1,3-interaction between the axial angular methyl group and the carboxyl group in dihydroiresin (XXVII). This inversion appears to occur prior to opening of the lactone ring, since it has been observed[38] that some isodihydroiresin can be isolated by direct chloroform extraction of the aqueous, alkaline solution before acidification.

VOL. 7 1959

We can turn now to a consideration of the absolute configuration of iresin, which was settled entirely by rotatory dispersion measurement.[39] In Fig. 1, there are reproduced the rotatory dispersion curves of 13-nor-3-dehydroisodihydroiresin (XI) and of its bromination product XVI together with those of 4α-methyldihydrotestosterone acetate (XX) and of 2α,6β-dibromo-4-methyltestosterone acetate (XXI). The latter two compounds represent standards of known absolute configuration and the relative configurations of the two pairs (XI vs. XX; XVI vs. XXI) are identical as far as the bicyclic systems are concerned. As has been demonstrated by us in a great number of examples,[39,40,41] this condition is sufficient—barring unusual conformational distortion—to produce identical signs and similar shapes of the rotatory dispersion curves if the relative and absolute configurations are identical. On the other hand, if the relative configurations are identical but the absolute configurations are opposite, then mirror image curves will be obtained and this is exactly the situation which is observed in Fig. 1. This is supported further by the rotatory dispersion data (see experimental) of 4-methyl-$\Delta^{1,4,6}$-androstatrien-17β-ol-3-one acetate (XXIV) and of the corresponding trienone XVII of the iresin series where Cotton effects of opposite sign are again observed. Other relevant rotatory dispersion curves are given in our earlier paper[2] and the entire rotatory dispersion evidence is overwhelmingly in favor

[38] Footnote 28 in ref. 5b.
[39] See C. Djerassi, *Bull. Soc. Chim. Fr.* 741 (1957) for earlier references to work carried out in our Laboratory on the relation of structure and rotatory dispersion of cyclic ketones.
[40] C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.* **80**, 3986 (1958).
[41] C. Djerassi, D. Marshall and T. Nakano, *J. Amer. Chem. Soc.* **80**, 4853 (1958).

of the absolute representation I, which is the mirror image of that found among the steroids and most of the higher terpenoids.

Iresin (I)[6] and its naturally occurring relatives[2] dihydroiresone (XXVI), dihydroiresin (XXVII) and isoiresin (XXVIII) represent the first group of sesquiterpenes which follow the isoprene skeleton XXIX. This particular bicyclofarnesol skeleton XXIX is found in virtually all of the di- and tri-terpenes and in demethylated form in the steroids. The discovery of iresin has thus afforded a missing link between the lower (mono- and sesqui-terpenes) and the higher ones. Subsequently, another sesquiterpene, drimenol (XXX), has been described[42] which also follows this isoprenoid pattern (XXIX), but it should be noted that its absolute configuration bears an antipodal relationship to iresin (I). The recent isolation of farnesiferol A[43] adds still another sesquiterpene to the iresin class and we have already speculated in another paper[9] on the possible biogenetic significance of this observation.

EXPERIMENTAL[44]

13-Nor-3-dehydroisodihydroiresin (XI)

(a) *From 3,13-bisdehydroisodihydroiresin* (XII). To a rapidly stirring solution of 2·74 g of isodihydroiresin (IX)[6] in 160 cc of acetone (distilled from permanganate) was added at room temp. 6·06 cc of an 8 N chromium trioxide–sulfuric acid solution.[16] After standing for a few min, 1 l. of water was added and the product extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated to dryness. Recrystallization of the residue from hexane–acetone afforded 1·72 g of the *keto aldehyde* XII, m.p. 184–189°, $[\alpha]_D$ +48°, $\lambda_{max}^{CHCl_3}$ 5·60, 5·75 and 5·85 μ. The substance gave no color with alcoholic ferric chloride. (Found: C, 68·26; H, 7·85; O, 23·78. $C_{15}H_{20}O_4$ requires: C, 68·16; H, 7·63; O, 24·21%).

The above keto aldehyde XII (1·72 g) was heated under reflux for 46 hr with 210 cc of conc HCl, 1 l. of water and 140 cc of ethanol and the volume was then reduced to one-half under reduced pressure. Extraction with chloroform, washing, drying and evaporating yielded an oily residue, which was dissolved in benzene and filtered through a short column (5·0 g) of alumina. Evaporation of the benzene solution and recrystallization from hexane–acetone furnished 710 mg of *13-nor-3-dehydroisodihydroiresin* (XI), m.p. 149–155. The analytical sample exhibited m.p. 153–155°,[45] $[\alpha]_D$ +8°, $\lambda_{max}^{CHCl_3}$ 5·61 and 5·84 μ, R.D. (Fig. 1) in methanol (*c*, 0·08): $[\alpha]_{700}$ +4·9°, $[\alpha]_{589}$ +4·9°, $[\alpha]_{365}$ −605°, $[\alpha]_{275}$ +1000°. (Found: C, 71·06; H, 8·56; O, 20·54. $C_{14}H_{20}O_2$ requires: C, 71·16; H, 8·53; O, 20·31%).

When 227 mg of the keto aldehyde XII was left at room temp for 30 hr with 1 N NaOH, the reaction mixture acidified and processed as above, there was isolated 36 mg of the desired nor-ketone XI, m.p. 150–154°. Chromatography of the mother liquors on either neutral or basic (pH 8–9) alumina yielded only recovered keto aldehyde.[17]

(b) *From 3-dehydroisodihydroiresin 13-trityl ether* (X). A solution of 500 mg of the trityl ether X[15] in 60 cc of dioxane and 50 cc of 20% H_2SO_4 was heated under reflux for 48 hr. The volume was reduced under diminished pressure, the dimedone derivative of formaldehyde (m.p. 190–192°) being isolated from the distillate, diluted with water and extracted with chloroform. Thorough washing of the chloroform solution with 1 N KOH removed all lactonic material, thus furnishing triphenyl carbinol upon drying and evaporating. The alkaline washes were acidified, extracted with chloroform, washed with water, dried and evaporated, leaving 180 mg of solid residue. Repeated recrystallization from hexane–acetone provided ca. 15% of the nor-ketone XI.

[42] C. J. W. Brooks and K. H. Overton, *Proc. Chem. Soc.* 322 (1957).
[43] L. Caglioti, H. Naef, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **41**, 2278 (1958).
[44] Melting points were determined on the Kofler block. Unless otherwise noted, rotations were measured in chloroform solution. We are indebted to Miss B. Bach for the infrared spectra and to Mrs. T. Nakano for the rotatory dispersion measurements. The microanalyses were carried out by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.
[45] At times, the melting point was 139–141° and we have found that this is not as satisfactory a criterion of purity as the very characteristic infrared absorption spectrum.

(c) *From* 13-*nor*-3-*dehydroiresin* (XIII).[46] A 56 mg sample of the nor-ketone XIII[25,12] was hydrogenated in 20 cc of ethyl acetate at room temp and atmospheric pressure in the presence of 50 mg of 5% palladized charcoal catalyst. Filtration of the catalyst after 1 hr, and evaporation to dryness left the crystalline 13-nor-3-dehydrodihydroiresin (XIV).[8] This was equilibrated without further purification by keeping at room temp for 20 hr in 7 cc of methanol containing 50 mg of KOH. Dilution with water, acidification with HCl, extraction with chloroform and evaporation left 33 mg of crystalline 13-nor-3-dehydroisodihydroiresin (XI), which exhibited m.p. 139–141°[8,45] after recrystallization from pentane–acetone. Identity was established by coincidence of the infrared spectra and rotatory dispersion curves with those of a specimen prepared according to procedure (a).

2-*Bromo*-13-*nor*-3-*dehydroisodihydroiresin* (XV)[19]

To a solution of 95 mg of the nor-ketone XI in 1·5 cc of glacial acetic acid containing a trace of hydrogen bromide was added dropwise a solution of 64 mg of bromine in 0·66 cc of acetic acid, the temperature being maintained around 40°. The colorless solution was diluted with 100 cc of water and the product was extracted with ether. Careful evaporation of the dried ether solution afforded an oil which solidified upon trituration with pentane. Leaching with ether and one recrystallization from hexane–acetone yielded 40 mg of the *bromo ketone* XV, m.p. 125–128°, $[\alpha]_D$ + 10°. The equatorial nature of the bromine atom was demonstrated by ultraviolet (λ_{max}^{EtOH} 292 mμ, log ε 2·12) and infrared ($\lambda_{max}^{CHCl_3}$ 5·60 and 5·75 μ) measurements when compared[20,21] with the corresponding values (λ_{max}^{EtOH} 293–295 mμ, log ε 1·49; $\lambda_{max}^{CHCl_3}$ 5·61 and 5·84 μ) of 13-nor-3-dehydroisodihydroiresin (XI). (Found: C, 52·83; H, 5·77. $C_{14}H_{19}BrO_3$ requires: C, 53·35; H, 6·08%).

2,6-*Dibromo*-Δ^4-13-*nor*-3-*dehydroisodihydroiresin* (XVI)

(a) *By dibromination.* The nor-ketone XI (200 mg) was dissolved in 3 cc of redistilled glacial acetic acid containing a small amount of hydrogen bromide and to this solution was added dropwise with vigorous stirring at room temp over a period of 1 hr 270 mg of bromine dissolved in 31 cc of acetic acid. After 3 hr at room temp, water was added to incipient cloudiness and the resulting precipitate was collected, washed well with water and dried; yield, 180 mg, m.p. 160° (dec), undepressed upon admixture with the material prepared according to (b), λ_{max}^{Nujol} 5·62 and 5·94 μ.

(b) *By tribromination.* The reaction was conducted with 472 mg of nor-ketone XI in 5 cc of glacial acetic acid (containing a small amount of hydrogen bromide) at 15°, the bromine solution (964 mg of bromine in 10 cc of acetic acid) being added rapidly with stirring. After standing for 1 hr at room temp, the bromine color still persisted and most of the dibromo ketone XVI had crystallized. Filtration, washing with water and careful drying at room temp *in vacuo* provided 427 mg of the *dibromo ketone* XVI, m.p. 154–157° (dec), $[\alpha]_D$ + 126° (dioxane), λ_{max}^{EtOH} 262–264 mμ, log ε 4·09, R.D. (Fig. 1) in dioxane (*c*, 0·10): $[\alpha]_{700}$ +96°, $[\alpha]_{589}$ +122°, $[\alpha]_{495-470}$ +174° (broad peak), $[\alpha]_{340}$ −650°, $[\alpha]_{305}$ +8295°. (Found: C, 43·51; H, 4·03; Br, 41·49. $C_{14}H_{16}Br_2O_3$ requires: C, 42·88; H, 4·11; Br, 40·75%).

$\Delta^{1,4,6}$-13-*Nor*-3-*dehydroisodihydroiresin* (XVII)

A solution of 619 mg of the dibromo ketone XVI in 20 cc of freshly distilled γ-collidine (Schweizerische Teerindustrie, Pratteln, Switzerland) and 10 cc of distilled dimethyl formamide was heated under reflux for 15 min, during which time the solution became dark colored and long needles appeared. After cooling, benzene was added and the precipitate of water-soluble collidine hydrobromide (562 mg, 88% yield for 2 molar equivalents) was filtered. The benzene–collidine filtrate was washed well with dilute HCl, dried and evaporated leaving 262 mg of a dark glass. Chromatography on 10 g of neutral alumina and elution with benzene provided 121 mg of crystalline solid (infrared spectrum practically identical with that of the analytical specimen), which was recrystallized to constant melting point from hexane–acetone; m.p. 164–168°, λ_{max}^{EtOH} 224, 250 (shoulder) and 296 mμ, log ε 4·16, 3·96 and 4·12, $\lambda_{max}^{CHCl_3}$ 5·60 (s), 6·01 (s), 6·09 (m), 6·16 (s), and 6·23 μ (w).[47] R.D.

[46] This experiment was performed by Dr. A. L. Nussbaum.

[47] For comparison, the infrared spectrum of $\Delta^{1,4,6}$-androstatrien-17β-ol-3-one acetate[26a] was measured under the same conditions and the following bands were noted in the relevant region: 6·00 (s), 6·08 (m), 6·15 (s) and 6·25 (shoulder).

in dioxane (*c*, 0·04): $[\alpha]_{700}$ −317°, $[\alpha]_{595}$ −568°, $[\alpha]_{398}$ −4368°, $[\alpha]_{365}$ −4477°, $[\alpha]_{313}$ −1605°, $[\alpha]_{303}$ −3182°. (Found: C, 73·25; H, 6·05. $C_{14}H_{14}O_3$ requires: C, 73·02; H, 6·13%).

2α,6β-Dibromo-4-methyltestosterone acetate (XXI)

(a) *From 4-Methyltestosterone acetate* (XXII). 4-Methyltestosterone acetate (XXII)[32] (100 mg) was dissolved in 3·5 cc of anhydrous ether containing one drop of acetic acid saturated with hydrogen bromide and cooled to 0°. A solution of 93 mg of bromine in 1·0 cc of acetic acid was added very rapidly with stirring and the colorless solution was concentrated immediately *in vacuo* without external heating. When the volume had been reduced about 70%, a colorless solid precipitated, which was filtered and washed well with ethanol; yield, 102 mg, m.p. 167–170° (dec), λ_{max}^{EtOH} 263·5 mμ, log ε 4·14, R.D. (Fig. 1) in dioxane (*c*, 0·09): $[\alpha]_{700}$ −52°, $[\alpha]_{589}$ −90°, $[\alpha]_{500-475}$ −121° (broad trough), $[\alpha]_{365}$ +283°, $[\alpha]_{300}$ −6072°. (Found: C, 52·23; H, 6·21; Br, 31·56. $C_{22}H_{30}Br_2O_3$ requires: C, 52·61; H, 6·02; Br, 31·83%).

(b) *From 4α-methyldihydrotestosterone acetate* (XX). A solution of 100 mg of 4α-methyldihydrotestosterone acetate (XX)[25,45] in 1·5 cc of glacial acetic acid and 0·5 cc of a saturated hydrogen bromide–acetic acid solution was cooled to just above the freezing point and 128 mg of bromine in 1·2 cc of acetic acid was added in less than 1 min with stirring. After 1 hr at room temp, there was still present some bromine color and dilution with aqueous methanol precipitated the white dibromo ketone XXI. Filtration and recrystallization from ethanol–chloroform led to 70 mg of colorless crystals, m.p. 165–167°, undepressed upon admixture with material prepared according to (a); the respective infrared spectra were also identical.

Dehydrobromination of 2α,6β-dibromo-4-methyltestosterone acetate (XXI)

(a) *With collidine–dimethyl formamide*. A solution of 1·03 g of the dibromo ketone XXI in 20 cc of γ-collidine and 15 cc of dimethyl formamide was heated under reflux for 15 min. Dilution with ether and filtration gave 520 mg (1·25 molar equivalents) of collidine hydrobromide and the filtrate was processed as described above for XVII, except that no chromatographic purification was required. Several recrystallizations of the crude dehydrobromination product from ethanol produced 100 mg of *2α-bromo-4-methyl-Δ[4,6]-androstadien-17β-ol-3-one acetate* (XXIII), m.p. 148°, then resolidifying and decomposing at 158–160°, λ_{max}^{EtOH} 294 mμ, log ε 4·26, $\lambda_{max}^{CHCl_3}$ 5·75, 5·96 (s), 6·14 (s), 6·28 (m), and 7·95 μ. R.D. in dioxane (*c*, 0·13): $[\alpha]_{700}$ +91°, $[\alpha]_{589}$ +152°, $[\alpha]_{398}$ +1850°, $[\alpha]_{323}$ −1230°, $[\alpha]_{325}$ −1110°. (Found: C, 62·28; H, 6·95; O, 11·18. $C_{22}H_{29}BrO_3$ requires: C, 62·72; H, 6·93; O, 11·40%).

(b) *With lithium carbonate and lithium bromide*.[35] A mixture of 350 mg of the dibromo ketone XXI, 10 cc of redistilled dimethyl formamide, 0·3 g of anhydrous lithium carbonate and 320 mg of fused lithium bromide was heated under reflux for 24 hr in an atmosphere of nitrogen. Dilution of the mixture with water precipitated a gum which was extracted with ether. After washing with water and drying, the ether was removed and all volatile material was distilled at 50° and 1 mm. The resulting tan-colored glass (150 mg) was dissolved in benzene and chromatographed on 15 g of neutral alumina. Elution with benzene afforded a small amount (ca. 10 mg) of the 2α-bromo-Δ[4,6]-3-ketone XXIII, while elution with 9:1 benzene–ether led to the desired *Δ[1,4,6]-4-methyl-androstatrien-17β-ol-3-one acetate* (XXIV), which resisted all attempts at crystallization; λ_{max}^{EtOH} 226, 255 (shoulder) and 306 mμ,[34] log ε 4·10, 3·84 and 4·04, $\lambda_{max}^{CHCl_3}$ 5.79 (s), 6.04 (m), 6.13 (m) and 6.23 μ (s); R.D. in dioxane (*c*, 0·137 at 700–397·5 mμ; 0·027 at 395–360 mμ; 0·013 at 355–342·5 mμ): $[\alpha]_{700}$ +1·4°, $[\alpha]_{589}$ +8·7°, $[\alpha]_{395}$ +710°, $[\alpha]_{342\cdot5}$ −1353°. (Found: C, 76·00; H, 8·30. $C_{22}H_{28}O_3$ requires: C, 77·61; H, 8·29%).

Since the analytical results were not very satisfactory—as had also been observed[8] with the oily Δ[1,4,6]-4-ethylcholestatrien-3-one—a sample was converted into the 2,4-*dinitrophenylhydrazone* using an ethanol–sulfuric acid solution of 2,4-dinitrophenylhydrazine. Passage of its benzene solution through a small column of alumina and recrystallization from ethanol gave ruby-red crystals, m.p. 247–249°; the ultraviolet absorption maximum ($\lambda_{max}^{CHCl_3}$ 412·5 mμ, log ε 4·52) occurred at the expected[9] position. (Found: C, 64·11; H, 6·24. $C_{28}H_{32}N_4O_6$ requires: C, 64·60; H, 6·20%).

[45] This sample showed m.p. 174–176°, $\lambda_{max}^{CHCl_3}$ 5·74, 5·80 and 7·92 μ, R.D. (Fig. 1) in methanol (*c*, 0·12): $[\alpha]_{700}$ −28°, $[\alpha]_{589}$ −28°, $[\alpha]_{365}$ +655°, $[\alpha]_{270}$ −1500°.

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VOL. 7 1959

THE CONFIGURATION OF CEVINE*†

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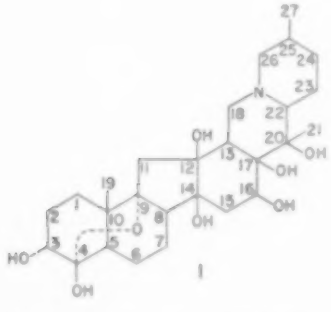
Abstract—The alkaloid cevine has been shown to have configuration II. The configurations of nine (C_3, C_4, C_5, C_9, C_{10}, C_{12}, C_{14}, C_{17}, C_{25}) of the fourteen asymmetric centers were established by earlier work. Hydrogenation of 16-dehydrocevine 3,4-diacetate (XIII) over platinum proceedeb stereoselectively to cevine 3,4-diacetate (XIV). Sodium borohydride reduction of 16-dehydrocevadine-D-orthoacetate-4-acetate (XVII) afforded a mixture of cevadine-D-orthoacetate 4-acetate (XVIII) and 16-epicevadine-D-orthoacetate 4-acetate (XVI). Both XVIII and XVI were submitted to alkaline hydrolysis followed by acid treatment to give cevagenine C-orthoacetate (XX) and 16-epicevagenine-C-orthoacetate (XIX). XIX consumed lead tetraacetate faster than XX, thereby indicating β-orientation for the C_{16} hydroxyl of cevine. Arguments are presented for assignment of configurations at C_8, C_{13} and C_{20}. Oxidation of veracevine-D-orthoacetate triacetate (XXII) with N-bromosuccinimide gave a bridged oxide (XXIII) which, in turn, afforded a formamido ketone (XXIV) on chromic anhydride-pyridine oxidation. The bridged β-oriented oxide structure of XXIII requires that the hydrogen at C_{22} be α-oriented.

THE currently accepted structure (I) for the extensively studied alkaloid cevine was first proposed in a classic collaborative paper in 1954.[1] Cevine has fourteen asymmetric centers: C_3, C_4, C_5, C_8, C_9, C_{10}, C_{12}, C_{13}, C_{14}, C_{16}, C_{17}, C_{20}, C_{22} and C_{25}. Previous studies in several laboratories have contributed to the partial elucidation of the configuration of cevine.[2–5] It is the purpose of this paper to present, in detail,



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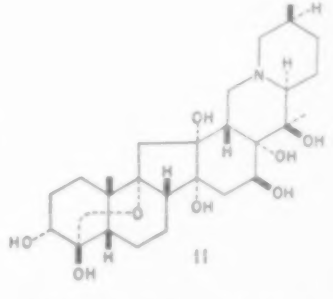


II

* This is Part XXXI of a series entitled "Veratrum Alkaloids"; Part XXX, S. M. Kupchan, *J. Amer. Chem. Soc.* **81**, 1925 (1959).

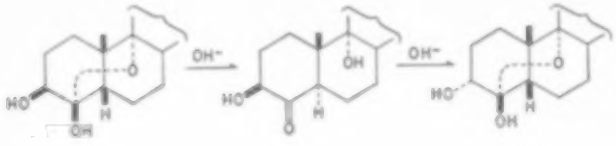
† The investigations which form the subject of this paper were first outlined in part in two preliminary communications. *J. Amer. Chem. Soc.* **78**, 3864 (1956); **80**, 1769 (1958). This work was supported in part by grants (H-2275, H-2952, A-2134) from the National Institute of Health, U.S. Public Health Service, from the National Science Foundation, and from the Sterling–Winthorp Research Institute.

‡ Deceased.

[1] D. H. R. Barton, O. Jeger, V. Prelog and R. B. Woodward, *Experientia* **10**, 81 (1954).
[2] D. H. R. Barton, C. J. W. Brooks and P. De Mayo, *J. Chem. Soc.* 3950 (1954).
[3] O. Jeger, V. Prelog, E. Sundt and R. B. Woodward, *Helv. Chim. Acta* **37**, 2302 (1954).
[4] F. Gautschi, O. Jeger, V. Prelog and R. B. Woodward, *Helv. Chim. Acta* **38**, 296 (1955).
[5] S. M. Kupchan, *J. Amer. Chem. Soc.* **77**, 686 (1955).

evidence for assignment of configuration at the remaining asymmetric centers of cevine which now can be represented completely by formula II.

The absolute configuration at C_{10} was shown to be identical with that (β-orientation) of C_{10} of the steroids through a masterful interrelationship of degradation products.[4] The orientations at C_3, C_4, C_5 and C_8 are related to C_{10} as shown in formula II by the steric requirements of the peculiar cage-like structure of the A/B system and the veracevine–cevagenine–cevine isomerizations,[1] depicted by formulas III–IV–V in the accompanying flow sheet. The configurations at C_{12}, C_{14} and C_{17}



III IV V

were related to C_9 *via* the cevagenine-D- and C-orthoacetates.[5] The structure of cevagenine-C-orthoacetate (XX) requires that the 12- and 14-hydroxyl groups have the same configuration as that at position 9, which is α-oriented (see above). The structure of the D-orthoacetates (e.g. XVIII and XXI) indicates the α-orientation of the 17-hydroxyl group as well, because of the common hinge (attached at C_{12} and C_{14}) of the orthoacetate residue in both the C and D orthoacetates. These conclusions received additional support from the demonstration that dihydrocevine-D-orthoacetate, which has a free α-hydroxyl group at C_9, is isomerized by acid to dihydrocevine-C-orthoacetate.[2] The configuration at C_{25} was established by partial synthesis of the piperidone VI from D-(+)-citronellal. This product was shown to be the antipode of the optically-active piperidone (VII) obtained by oxidation of cevine.[3]

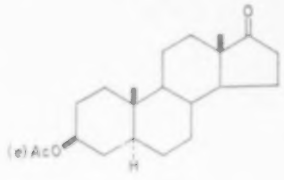
VI VII

Configuration at C_{16}. Prior to the present study the hydroxyl group at this position was assigned the α-*equatorial*-orientation. This assignment was made on the basis of the ready methanolysis of compounds acetylated at this position.[1,2]

The susceptibility of the C_{16} acetate esters to base catalyzed[6] methanolysis appeared to us to be abnormally high even for an equatorial ester. This rate of methanolysis, indeed, was found to exceed that of an *unhindered* equatorial ester. Wheras cevadine-D-orthoacetate 4,16-diacetate[7] (XV) underwent methanolysis in 75 per cent yield after 20 hr in dilute methanol, epiandrosterone-3-*equatorial-acetate* (VIII) was recovered largely (75 per cent) unchanged after similar treatment in the presence of cevine to serve as the basic catalyst. In the germine series the C_7 acetate, which is

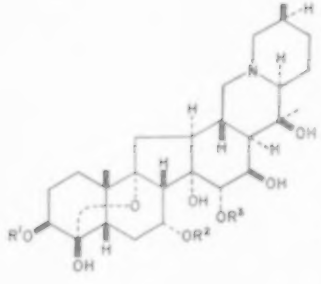
[6] W. J. Rosenfelder, *J. Chem. Soc.* 2638 (1954).
[7] A. Stoll and E. Seebeck, *Helv. Chim. Acta* **35**, 1942 (1952).

undoubtedly α-*axially*-oriented[8] exhibits reactivity comparable with the C_{16} acetate in the cevine derivatives. The facile methanolysis of germitrine [IX:R^1 = (l)-2-methylbutyric acid (MB); R^2 = Ac; R^3 = (d)-2-hydroxyl-2-methyl butyric acid (HMB)] to germerine (IX: R^1 = MB; R^2 = H; R^3 = HMB)[9,10] and of neo-germitrine (IX: $R^1 = R^2$ = Ac; R^3 = MB) to germidine[10,11] (IX: R^1 = Ac; R^2 = H; R^3 = MB) are noteworthy examples of this phenomenon. These two cases were discovered in the search for the cause of the remarkable loss in hypotensive activity which accompanies the methanolysis of the C_7 acetate group of the naturally

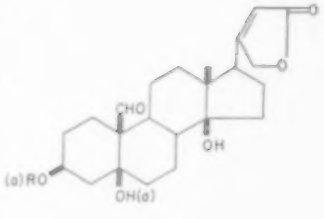


VIII

occurring germine esters.[9,11] This unusual behavior prompted us to postulate a facilitation of methanolysis by a neighboring hydroxyl group (at C_{14} in these two cases) bearing a *cis*-1,3-di*axial* relationship to the ester group and thus juxtaposed for participation. This hypothesis was tested by treatment of strophanthidin 3-acetate (X: R = Ac) with dilute methanol and cevine for twenty hours; strophanthidin (X: R = H) was isolated in 66 per cent yield. Henbest and Lovell have also independently presented convincing demonstrations of this effect in the sterol series and have discussed mechanistic interpretations.[12]



IX



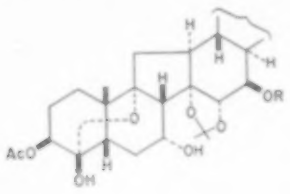
X

The C_{16} acetate in the germine series also exhibits abnormal susceptibility to methanolysis. Germine 14,15-acetonide 3,16-diacetate (XI: R = Ac) is readily methanolyzed to germine 14,15-acetonide 3-acetate (XI: R = H),[8] and germine 3,4,7,15,16-pentaacetate (XII: R = Ac) is rapidly transformed by methanol to the 3,4,7,15-tetraacetate (XII: R = H).[10] Now the C_{16}-acetoxy group is evidently

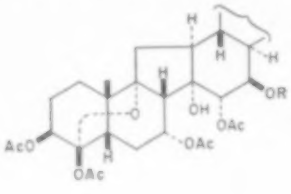
[8] S. M. Kupchan and C. R. Narayanan, *J. Amer. Chem. Soc.* **81**, 1913 (1959).
[9] J. Fried, H. L. White and O. Wintersteiner, *J. Amer. Chem. Soc.* **72**, 4621 (1950).
[10] S. M. Kupchan, *J. Amer. Chem. Soc.* **81**, 1921 (1959).
[11] J. Fried, P. Numerof and N. H. Coy, *J. Amer. Chem. Soc.* **74**, 3041 (1952).
[12] H. B. Henbest and B. J. Lovell, *Chem. & Ind.* 278 (1956); *J. Chem. Soc.* 1965 (1957).

β-axially-oriented,[8] which requires, on the basis of a 1,3-di*axial* facilitation, a *β-axial*-orientation of the C_{20} hydroxyl. It is therefore attractive to postulate identical disposition of the C_{16} and C_{20} hydroxyl groups in cevine. The following experiments establish this point.

Hydrogenation of 16-dehydrocevine 3,4-diacetate[2] (XIII) over platinum proceeded stereoselectively to give cevine 3,4-diacetate (XIV). The molecular model of the ketone shows that the α- is much less hindered than the β-face for approach to the catalyst, which suggests that reaction would proceed to give a β-oriented hydroxyl.

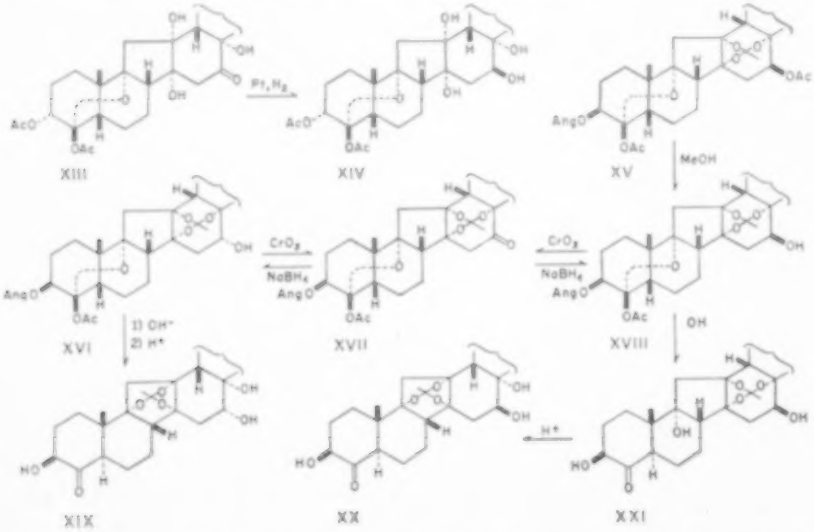


XI



XII

Sodium borohydride reduction of 16-dehydrocevadine-D-orthoacetate-4-acetate[2] (XVII) afforded a mixture of cevadine-D-orthoacetate-4-acetate (XVIII)[7] and 16-epicevadine-D-orthoacetate-4-acetate (XVI). The structure of XVI was confirmed by oxidation with chromic acid to regenerate the original ketone (XVII). In order to liberate the C_{17}-hydroxyl group, both epimeric D-orthoacetates were submitted to alkaline hydrolysis followed by treatment with mineral acid to effect rearrangement to the C-orthoacetates.[5] 16-Epicevagenine-C-orthoacetate (XIX) was found to react



XIII XIV XV XVI XVII XVIII XIX XX XXI

with lead tetraacetate at a strikingly faster rate than cevagenine-C-orthoacetate (XX), which suggests that the hydroxyl groups at C_{16} and C_{17} are *cis*-disposed in the former and *trans*- in the latter. Since the C_{17} hydroxyl group is undoubtedly α-oriented (see above), the configurations are established as XIX and XX, respectively.

Configuration at C_8, C_{13} *and* C_{20}. Now with the establishment of the β-configuration of the C_{16} hydroxyl group in cevine, the β-configuration may be assigned to the C_{20} hydroxyl group—a point concerning which there has been considerable doubt.[2,4,13] The *cis*-1,3-di*axial* disposition of the C_{16} and C_{20} hydroxyl groups requires, in turn, that rings D and E be *trans*-fused, which, in view of the established α-orientation of the hydroxyl group at C_{17} (see above) requires β-orientation of the hydrogen at C_{13}. A similar argument has been advanced with regard to the orientation at C_8 in germine, namely that the *cis*-1,3-di*axial* relationship of the substituents at C_7 and C_{14} requires that the hydrogen at C_8 be β-oriented.[8] At each of the asymmetric carbon atoms common to both veracevine and germine which have been discussed up to this point (C_3, C_4, C_5, C_9, C_{10}, C_{13}, C_{14}, C_{16}, C_{17}, C_{20}) the configurations at the common asymmetric carbon atoms are identical. It is considered reasonable to assume that the configuration at C_8 in cevine is the same as that in germine and all other naturally occurring steroids.

VOL. 7 1959

We have noted that the C_{16}-hydroxyl group of 16-epicevadine-D-orthoacetate 4-acetate (XVI) is relatively resistant to acetylation. This fact is consistent with the α-*equatorial*-configuration for the methyl group at C_{20} which is held rigidly eclipsed with the C_{16} α-hydroxyl group and accordingly exerts serious crowding.

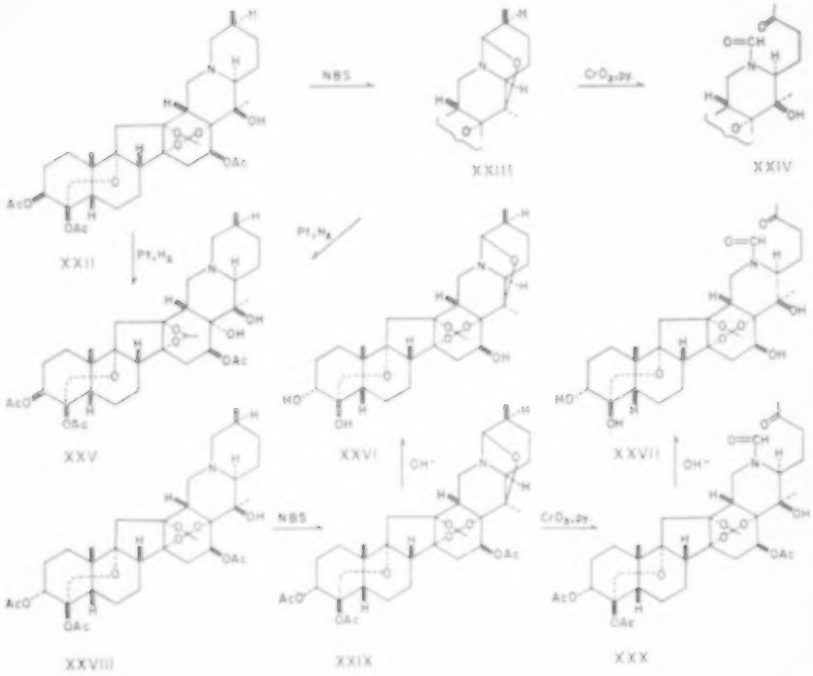
Configuration at C_{22}. The foregoing considerations provide a basis for assigning configurations to thirteen of the fourteen asymmetric centers of cevine. Only the assignment of the configuration at C_{22} remained, and this proved to be our most difficult task.

In the hope of obtaining a carbinolamine for hydrogenation studies (of the iminium salt), veracevine D-orthoacetate triacetate[14] (XXII) was oxidized with N-bromosuccinimide.[15] A dehydro compound was obtained which evidently has the bridged oxide structure XXIII for the following reasons. (1) The infrared spectrum of the dehydro compound in Nujol showed no absorption in the hydroxyl region. (2) The 16-acetate group survived prolonged treatment with methanol and triethylamine, an indication of the absence of an *axial* hydroxyl at C_{20} to facilitate methanolysis (see above). (3) That the N-bromo-succinimide reaction did not lead to introduction of a carbonyl group was demonstrated as follows. Because XXIII would be expected to isomerize to the 4-keto compound (see formulas III — IV), it was considered necessary to operate in the alkali-stable cevine series. Cevine D-orthoacetate triacetate (XXVIII) was oxidized with N-bromo-succinimide to give an entirely analogous dehydrocevine D-orthoacetate triacetate (XXIX). Alkaline hydrolysis of XXIX afforded dehydrocevine D-orthoacetate (XXVI) the infrared spectrum of which exhibited no absorption in the carbonyl region. (4) Chromium trioxide–pyridine oxidation of XXIII afforded a neutral product in 35 per cent yield, evidently the formamido ketone XXIV (see below). The same formamido ketone was obtained directly in 12 per cent yield by similar oxidation of XXII.

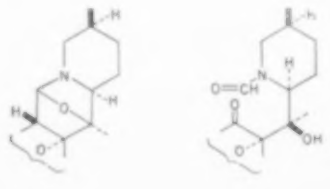
The structure of the formamido ketone was shown to be XXIV as follows. Upon exhaustive acid-catalysed hydrolysis XXIV yielded five mole-equivalents of volatile acid; one mole-equivalent of formic acid was found among the acids formed. The

[13] K. Macek and Z. J. Vejdelek, *Nature, Lond.* **176,** 1173 (1955); *Coll. Czech. Chem. Comm.* **22,** 253 (1957).
[14] S. M. Kupchan, D. Lavie, C. V. Deliwala and B. Y. A. Andoh, *J. Amer. Chem. Soc.* **75,** 5519 (1953).
[15] O. E. Edwards, F. H. Clarke and B. Douglas, *Canad. J. Chem.* **32,** 235 (1954).

infrared spectrum of XXIV showed a band at 6·07 μ attributable to the formamido grouping. In order to detect whether a carbonyl group was introduced in the course of the chromium trioxide oxidation, we elected to study the alkali stable (see above) cevine analog. Oxidation of XXIX with chromium trioxide–pyridine gave the corresponding formamido ketone (XXX). This substance gave a monosemicarbazone. Alkaline hydrolysis of XXX gave the desacetyl–formamido–ketone XXVII. In addition to the amide band at 6·07 μ, the infrared spectrum of XXVII exhibited normal ketone absorption at 5·85 μ.



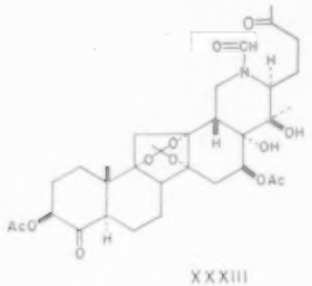
The evidence presented thus far supports an oxide structure for the products of N-bromosuccinimide oxidation and a formamido ketone structure for the products of chromium trioxide–pyridine oxidation. The alternative partial formulations XXXI and XXXII for the respective products may be excluded on the basis of the following



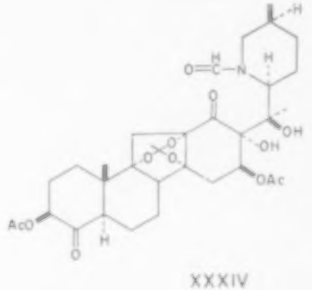
XXXI XXXII

VOL. 7 1959

evidence.* (1) The formamido ketone derived from cevine *readily* formed a semicarbazone. This behavior is consistent with structure XXX which is expected to show normal ketone reactivity, but not with tetrasubstituted ketone structure XXXII which would be expected to react very slowly, if at all. (2) The formamido-ketone showed active methylene group reactivity in the Zimmermann test.[16] (3) Upon treatment in alkaline solution with furfural the formamido-ketone gave an amorphous product, λ_{max} 318 mμ, characteristic of a furfurylidene ketone.[17] (4) The formamido-ketone derived from cevagenine-C-orthoacetate diacetate[14] was, like the parent alkaloid, stable to lead tetraacetate. The compound with structure XXXIII is expected to show this stability because the integrity of the rigid *trans* di*axial* glycol system at C_{17}, C_{20} is maintained during cleavage of Ring F. A product with structure XXXIV, on the other hand, would be expected to cleave readily with glycol-splitting reagents.



XXXIII



XXXIV

(5) Nuclear magnetic resonance spectroscopy† studies afforded direct evidence that the formamido ketone was a methyl ketone. The substances examined were only sparingly soluble in chloroform of carbon disulfide; hence pyridine was used as the solvent and water (contained in a separate capillary tube) was employed for reference.‡ The spectra of cevine D-orthoacetate[18] and of the corresponding dehydro compound XXVI exhibited a family of appropriate sharp signals above +217 c.p.s. (relative to benzene, i.e., water = +70 c.p.s.) corresponding to the four methyl groups. A detailed analysis of these spectra will be recorded in a future publication. Noteworthy to the case at hand is the fact that the spectrum of the corresponding formamido ketone XXVII exhibited a sharp signal, characteristic of methyl proton resonance, at +200 c.p.s. (+170 c.p.s. corrected for chloroform solution) which corresponds to

* The iodoform test on the formamido ketone was negative in our hands. This evidence was inconclusive, particularly in view of the fact that the test failed also with 3α-acetoxypregnane-11,20-dione.

† The spectra were determined at 40 megacycles/second with a Varian Associates V-4300-B High Resolution NMR Spectrometer having a 12-in. Magnet System equipped with a V-K 3506 Flux Stabilizer. We wish to thank K. L. Williamson for determining these spectra.

‡ Control experiments with related substances of known constitution showed that, under the conditions employed here, NMR signals obtained from pyridine solutions of the compounds in question could be corrected to chloroform or carbon disulfide solutions by subtracting ca. 30 c.p.s. It is to be noted that pyridine has not been considered to be a reliable standard solvent for NMR spectroscopy, N. F. Chamberlain, *Analyt. Chem.* **31**, 56 (1959).

[16] W. Zimmermann, *Z. Phys. Chem.* **233**, 257 (1935); D. H. R. Barton and P. De Mayo, *J. Chem. Soc.* 887 (1954).

[17] W. S. Johnson, B. Bannister and R. Pappo, *J. Amer. Chem. Soc.* **78**, 6331 (1956).

[18] D. H. R. Barton, C. J. W. Brooks and J. S. Fawcett, *J. Chem. Soc.* 2137 (1954).

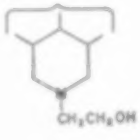
the methyl group of a methyl ketone.[19] The spectra of the precursor compounds showed no significant absorption in the +200 c.p.s. region.

The bridged β-oriented oxide structure of the dehydro bases requires that the hydrogen at C_{22} be α-oriented (see formula XXXVIII). That the stereochemical integrity of the molecule was preserved during the oxide formation was demonstrated by catalytic hydrogenation of XXIII over platinum in acetic acid. Two mole-equivalents of hydrogen was absorbed to give a substance identical with the product of hydro-genation (one mole equivalent uptake) of XXII, namely veracevine-D-dihydro-orthoacetate triacetate.*

It is of interest to note that the orthoacetate cage structure is not required for production of the stable bridged carbinolamine ether. Thus cevine triacetate[18] was oxidized with N-bromosuccinimide to a dehydrocevine triacetate entirely analogous to the substance XXIII in the orthoacetate series. The further conversion with chromium trioxide–pyridine to a formamido ketone (cf. formula XXIV) was also effected. The properties of these products closely resembled their counterparts in the orthoacetate series.

On the basicity of the carbinolamine ether. Carbinolamine ethers of the type $ROCNR_2$, like the free carbinolamines, would be expected *a priori* to exhibit basicity significantly stronger than that of a tertiary amine, because protonation on oxygen leads to a structure, $ROCNR_2$, that can cleave to give the alcohol (ROH) plus the stable ternary iminium cation, $>C=NR_2\oplus$. Thus the carbinolamine ether system (shown, in part, by formula XXXV) of veatchine (p*K*a′ 11·5) and of its isomer garryine (p*K*a′ 8·7) is responsible for enhanced basicity in these alkaloids as compared with the corresponding amino alcohol XXXVI (p*K*a′ 6·85).[20]

XXXV



XXXVI

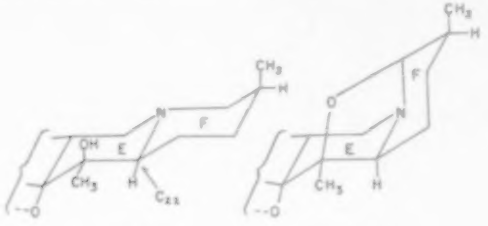
If, however, cleavage to the ternary iminium salt were inhibited, the carbinolamine ether would be expected to exhibit relatively weak basic properties because of the electron withdrawing inductive effect of the ether–oxygen atom on the neighboring nitrogen atom. The bridged-oxido dehydro bases (XXIII, XXIX) of the present work appear to be the first examples of such carbinolamine ethers that are resistant to cleavage to iminium salts by acid. Thus the perchlorate of dehydroveracevine-D-orthoacetate triacetate (XXIII) failed to show the infrared absorption characteristic

* This product is analogous to that produced by hydrogenation of cevine-D-orthoacetate triacetate (cf. 21).

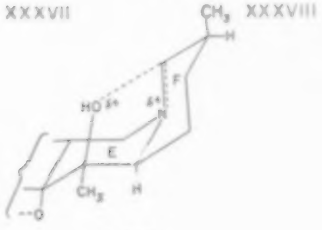
[19] Cf. the value of +171 ± 1 c.p.s. in chloroform, J. N. Shoolery and M. T. Roberts, *J. Amer. Chem. Soc.* **80**, 5121 (1958).

[20] K. Wiesner, S. K. Figdor, M. F. Bartlett and D. R. Henderson, *Canad. J. Chem.* **30**, 608 (1952); K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, *J. Amer. Chem. Soc.* **76**, 6068 (1954).

of ternary iminium salts and failed to undergo substitution by cyanide ion.[21] In accordance with expectation, the basicity of XXIII (cf. XXXVIII) (p*K*a′ 3·8) was strikingly weak compared with that of the alkaloid XXII (cf. XXXVII) (p*K*a′ 7·4).* It is not known whether the proton prefers residence on the oxygen or the nitrogen atom in the salts of these bridged ring oxido-bases, but their unusual stability may be attributed to unfavorable bond angles (in violation of Bredt's rule) required in the transition state for formation of the iminium cation (see formula XXXIX). The foregoing is not meant to imply preclusion of the possibility that the barrier of this high energy transition state can be surmounted under appropriate conditions.



XXXVII XXXVIII



XXXIX

It should be noted that carbinolamine ethers with basicities slightly diminished from those of closely related amines are known among the solanum[22] and the aconite[23] alkaloids. The small diminution in basicity in each of the latter cases is evidently not due to extreme stability of the carbinolamine ether systems, for infrared spectroscopy has shown that corresponding salts in each case have iminium structures.[23,24]

EXPERIMENTAL†

Methanolysis of epiandrosterone acetate

Epiandrosterone acetate [25] (1 g). m.p. 110–112°, was dissolved in methanol (25 ml) and water (5 ml), and cevine (1 g) was added to the solution. After 21 hr at room temp, acetic acid (4 ml) and water (5 ml) were added and the methanol was removed by distillation at reduced pressure. The aqueous suspension was extracted thoroughly with chloroform. The chloroform extract was washed

* The p*K*a′ values were determined by potentiometric titration with 0·1 N $HClO_4$ in 80% methylcellosolve by Drs. T. Higuchi and K. Connors to whom we extend our thanks.

† Melting points are corrected for stem exposure. Values of $[\alpha]_D$ have been approximated to the nearest degree. Ultraviolet absorption spectra were determined on a model 11 MS Cary recording spectrophotometer and 95% ethanol was used as solvent. Infrared spectra were determined on a Baird Model B double beam infrared recording spectrophotometer, and unless otherwise specified chloroform was used as solvent. Microanalyses were carried out by Dr. S. M. Nagy and his associates at Massachusetts Institute of Technology on samples dried at reduced pressure at 110°.

[21] Cf. N. J. Leonard and F. P. Hauck, Jr., *J. Amer. Chem. Soc.* **79**, 5279 (1957).
[22] H. Bloom and L. H. Briggs, *J. Chem. Soc.* 3591 (1952).
[23] K. Wiesner, S. Ito and Z. Valenta, *Experientia* **14**, 167 (1958).
[24] E. Schlittler and H. Uehlinger, *Helv. Chim. Acta* **35**, 2034 (1952).
[25] Footnote 29 on ref. 17.

with dilute acetic acid, then with water, and evaporated to dryness. Crystallization of the residue from methanol–water yielded starting material (750 mg), m.p. 107–109°. The infrared spectrum was identical with that of authentic epiandrosterone 3-acetate.

Methanolysis of strophanthidin 3-acetate

Strophanthidin 3-acetate[24,25] (400 mg) m.p. 248–250°, was dissolved in methanol (15 ml) and water (5 ml), and cevine (400 mg) was added. After 21 hr at room temp acetic acid (3 ml) and water (5 ml) were added, and the methanol was evaporated at reduced pressure. The aqueous suspension was extracted thoroughly with chloroform. The chloroform extract was washed with dilute acetic acid, then with water and evaporated to dryness. The residue was crystallized from methanol–water to give 242 mg of strophanthidin, m.p. 170–175° after softening at 160°, undepressed on admixture with authentic strophanthidin, m.p. 171–177° after softening at 163°. The infrared spectra of the two samples were identical.

Hydrogenation of 16-*dehydrocevine* 3,4-*diacetate*

16-Dehydrocevine 3,4-diacetate[2] (100 mg), m.p. 275–277° dec. in glacial acetic acid (15 ml) was hydrogenated over 30 mg of platinum oxide catalyst at room temp and atmospheric pressure. One mole-equivalent of hydrogen was absorbed in 15 min and no further uptake was observed during the next 30 min. The mixture was filtered, dilute ammonia was added to pH 9, and the solution was extracted thoroughly with chloroform. The residue obtained on evaporation was crystallized from ether–petroleum ether (b.p. 40–60°) to yield needles (68 mg), m.p. 274–277° dec. undepressed on admixture with authentic cevine 3,4,-dicaetate,[2] m.p. 275–278° dec. The infrared spectra of the two samples were identical.

Sodium borohydride reduction of 16-*dehydrocevadine*-D-*orthoacetate* 4-*acetate*

A solution of 16-dehydrocevadine-D-orthoacetate 4-acetate[2] (3·2 g), m.p. 268–270° dec. in hot methanol (800 ml) was treated with sodium borohydride (1·6 g) and allowed to stand for 45 min. Additional sodium borohydride (1·6 g) was added and the solution was allowed to stand for 1 hr. Acetic acid (8 ml) was added and the solution was concentrated at reduced pressure to a volume of 50 ml. Water (30 ml) was added and the remaining methanol evaporated at reduced pressure. The aqueous solution was adjusted to pH 9 with dil ammonia and extracted with chloroform. The chloroform solution was concentrated (approximately 10 ml), 95% ethanol (20 ml) was added, and concentration continued until crystallization began. Filtration afforded needle clusters (1·15 g), m.p. 305–307° dec. Recrystallization of a 400 mg sample by dissolution in a large volume of boiling 95% ethanol, filtering, and then concentrating the filtrate, gave 230 mg of 16-epicevadine-D-orthoacetate 4-acetate as colorless needles, m.p. 314–316° dec. $[\alpha]_D^{27} +65°$ (*c*, 1·17, chf.). (Found: C, 66·21; H, 7·96. Calcd. for $C_{34}H_{51}O_9N$: C, 66·31, H, 8·02%).

The mother liquor of the 1·15 g fraction, after concentration, gave 370 mg (second crop), m.p. 280–283° dec. Evaporation of the mother liquor to dryness and crystallization of the residue from acetone–water gave 180 mg (third crop), m.p. 276–279° dec. The infrared spectra of the second and third crops showed that these fractions consisted largely of cevadine-D-orthoacetate 4-acetate.

16-*Epiceragenine-C-orthoacetate* (XIX)

16-Epicevadine-D-orthoacetate 4-acetate (XVI, 1·15 g), m.p. 305–307° dec. in 15 ml of 5% methanolic KOH was heated under reflux for 30 min. Water (15 ml) was added, the methanol was evaporated at reduced pressure, and the aqueous suspension was extracted with chloroform. The chloroform was evaporated and the residue dissolved in 5% H_2SO_4. After 15 min at room temp the pH was adjusted to 9 with dilute ammonia and the solution was extracted with chloroform. The residue obtained on concentration was crystallized from benzene–ether to yield needles (370 mg), m.p. 255–263° dec. after melting initially at 220–230° and resolidifying at 230–235°. This product

* We thank Dr. M. Ehrenstein of the University of Pennsylvania and Dr. W. G. Bywater of S. B. Penick and Co. for samples of strophanthin from which strophanthidin was obtained for this work. We also thank S. B. Penick and Co. for a generous gift of veratrine.

[25] T. Reichstein and H. Rosenmund, *Pharm. Acta Helv.*, **15**, 150 (1940).

was dissolved in chloroform and chromatographed on Woelm "neutral" alumina (8 g). The fractions from elution with 90 ml of chloroform were combined and crystallized from benzene–95% ethanol to give 120 mg of 16-epicevagenine-C-orthoacetate as colorless needles containing one mole-equivalent of benzene of crystallization, m.p. 276–279° dec. $[\alpha]_D^{22}$ −10° (*c*, 1·22, chf.); λ_{max} 239 mμ, 249 mμ (ε 250), 261 mμ. (Found: C, 69·09; H, 7·81. Calcd. for $C_{29}H_{43}O_8N{\cdot}C_6H_6$: C, 68·66; H, 8·07%).

*Lead tetraacetate titrations**

Fifteen to twenty mg samples of compounds to be examined were dissolved in acetic acid (1 ml), 2 ml of approximately 0·06 N lead tetraacetate in acetic acid was added and then the solution was diluted to 10 ml with acetic acid. At noted intervals 1 ml aliquots were drawn out and titrated according to the procedure of Hockett and McClenahan.[27] The results obtained with the epimeric cevagenine-C-orthoacetates are summarized in Table 1.

VOL. 7 1959

TABLE 1. LEAD TETRAACETATE TITRATIONS

Time (hr)	Mole-equivalents consumed by cevagenine-C-orthoacetate	Mole-equivalents consumed by 16-epicevagenine-C-orthoacetate
0·15	0·0	0·9
0·5	0·0	1·0
0·65	0·0	1·1
5	0·4	1·4
10	0·8	1·6
15	0·9	1·7
24	1·4	1·8

Dehydroveracevine-D-*orthoacetate triacetate* (XXIII)

Veracevine-D-orthoacetate triacetate[14] (4 g), m.p. 254–256° dec. in chloroform (50 ml) was treated with a solution of N-bromosuccinimide (1·5 g) in chloroform (125 ml) and the mixture was allowed to stand at room temp for 5 min. The solution was washed thoroughly with cold, dil ammonium hydroxide, then with water and evaporated to dryness under reduced pressure. Crystallization of the residue from aqueous acetone afforded colorless needles (1·39 g), m.p. 267–268° dec. Purification was effected by adsorption of the product (2·3 g) in chloroform on Woelm "neutral" alumina (50 g) and elution with chloroform (ten 50 ml fractions). Fractions 2–7 afforded oils which crystallized from ether (m.p. 275–277° dec.). Recrystallization from aqueous acetone gave colorless prismatic needles (1·8 g), m.p. 279–280° dec.

A preparation of comparable purity was obtained by oxidative purification of the crude product, m.p. 267–268°. A solution of the product (300 mg) in acetic acid (5 ml) was treated with 0·65 N chromium trioxide in 98·5% acetic acid (5 ml) and the mixture was allowed to stand at room temp for 1 hr. Cold water, excess dilute sodium bisulfite solution and ammonium hydroxide were added to adjust the pH to 9 and the solution was extracted with chloroform. The residue obtained on evaporation at reduced pressure was crystallized from aqueous acetone to yield needles (240 mg), m.p. 279–281° dec. Recrystallization from the same solvents gave colorless prismatic needles, m.p. 280–282° dec. $[\alpha]_D^{25}$ +33° (*c*, 1·88 diox). (Found: C, 63·51; H, 7·35; acetyl, 25·52. Calcd. for $C_{35}H_{47}O_{11}N$: C, 63·90; H, 7·20; acetyl, 26·17%).

The perchlorate was prepared in methanol and crystallized upon dilution with water as colorless prisms, m.p. 222–224° dec. The salt decomposed upon attempted recrystallization. It showed no infrared absorption characteristic of ternary iminium salts and dehydroveracevine-D-orthoacetate triacetate was recovered unchanged after treatment with aqueous potassium cyanide solution.[21]

* Experiment by Miss Arlene G. Gardner.

[27] R. C. Hockett and W. S. McClenahan, *J. Amer. Chem. Soc.* **61**, 1670 (1939).

The methiodide was prepared by treatment of the dehydro base (400 mg) in methanol (10 ml) with methyl iodide (2 ml) at room temp. After 12 hr the solution was evaporated at reduced pressure and the residue was crystallized from aqueous acetone giving 150 mg of starting material. The acetone was evaporated, water and ammonium hydroxide were added, and the suspension was extracted with chloroform. The residue obtained by evaporation of the chloroform was crystallized from aqueous acetone to give colorless needles (180 mg), m.p. 236–239° dec. Recrystallization from the same solvents gave the methiodide, m.p. 244° dec. $[\alpha]_D^{25}$ +62° (*c*, 2·00, py.). (Found: C, 52·67; H, 6·48; N-methyl, 2·08. Calcd. for $C_{36}H_{56}O_{11}NI \cdot H_2O$: C, 52·88; H, 6·41; N-methyl, 1·84%).

Attempted methanolysis of dehydroveracevine-D-*orthoacetate triacetate*

A solution of the dehydro base XXIII (250 mg) in methanol (300 ml) and triethylamine (0·1 ml, ca. two mole-equivalents) was left at room temp for 20 hr. Evaporation to dryness under reduced pressure and crystallization from aqueous acetone gave 225 mg of starting material, m.p. 277–279° dec. undepressed on admixture with a sample of starting material. The infrared spectra (potassium bromide pellet) of the two samples were identical.

Dehydrocevine-D-*orthoacetate triacetate* XXIX

A solution of cevine-D-orthoacetate triacetate[25] (6 g), m.p. 300–303° dec. in chloroform (100 ml) was treated with a solution of N-bromosuccinimide (2 g) in chloroform (200 ml) and the mixture was allowed to stand at room temp for 30 min. The product was isolated as described above for XXIII and the residue from chloroform crystallized readily from acetone giving plates (3·1 g), m.p. 256–257° dec. Recrystallization from acetone afforded glistening plates, m.p. 256–257° dec. $[\alpha]_D^{25}$ +58° (*c*, 2·00, py.). (Found: C, 63·62; H, 7·44; acetyl, 25·36. Calcd. for $C_{35}H_{47}O_{11}N$: C, 63·90; H, 7·20; acetyl, 26·17%).

Dehydrocevine-D-*orthoacetate* XXVI

Dehydrocevine orthoacetate triacetate (XXIX, 2 g), m.p. 256–257° dec. was dissolved in 20% alcoholic KOH (20 ml) and the solution was heated under reflux for 30 min. Water (20 ml) and acetic acid (4 ml) were added, whereupon a colorless crystalline solid separated. Recrystallization of the solid from methanol afforded: first crop, 400 mg, m.p. 283–284° dec. second crop, 110 mg, m.p. 271–274° dec. third crop, 106 mg, m.p. 245–260° dec. An additional 61 mg, m.p. 266–272° dec. was obtained by chloroform extraction of the mother liquors of the first crude crystalline solid described above. All of the crystalline crops were combined and recrystallized from methanol to yield 525 mg of colorless needles, m.p. 283–284° dec. $[\alpha]_D^{25}$ +3° (*c*, 2·00, py.). (Found: C, 65·41; H, 7·93; acetyl, 6·97. Calcd. for $C_{29}H_{41}O_8N$: C, 65·52; H, 7·78; acetyl, 8·10%).

Formamido ketone (XXIV) *derived from veracevine*-D-*orthoacetate triacetate*

(a) *From veracevine*-D-*orthoacetate triacetate.* Veracevine-D-orthoacetate triacetate[14] (7 g), m.p. 254–256° dec. in pyridine (75 ml) was added to the complex prepared from chromium trioxide (14 g) and pyridine (140 ml). The mixture was allowed to stand for 40 hr at room temp with occasional shaking. Water (300 ml), chloroform (400 ml) and dilute ammonia (75 ml of 1 : 1) were added and the mixture was shaken and filtered through a bed of Filtercel. The chloroform layer was washed with water and evaporated on the steam bath at reduced pressure. The highly colored residue was dissolved in acetone–petroleum ether (b.p. 40–60°), filtered to remove some red-brown insoluble solid material, and cooled. The crystalline product thus obtained was recrystallized from benzene to give colorless needles (1·06 g), m.p. 263–264° dec. $[\alpha]_D^{27}$ +54° (*c*, 2·02, diox.); λ_{max} 6·07 μ (N—C—O). (Found: C, 60·59; H, 7·17. Calcd. for $C_{35}H_{47}O_{12}N$: C, 60·94; H, 6·87%).

In a volatile acid determination[29] 19·95 mg of the formamido ketone yielded an amount of acid equivalent to 37·15 ml of 0·003999 N sodium thiosulfate; calculated for four mole-equivalents of acetic acid and one mole-equivalent of formic acid, as expected for structure XXIV, 36·16 ml. Formic acid formed during acid hydrolysis of the formamido ketone was determined by reduction of

[28] A. Stoll and E. Seebeck, *Helv. Chim. Acta* **36**, 189 (1953).

[29] J. B. Niederl and V. Niederl, *Micromethods of Quantitative Organic Analysis* pp. 257–262. John Wiley, New York (1942).

mercuric chloride and gravimetric determination of the calomel formed.[28] (Found: 0·88 mole-equivalent).

Tests for active methylene group reactivity were run as follows: (1) A Zimmermann test[16] was run by treating the formamido ketone (ca. 1 mg) in 2 N alcoholic potassium hydroxide (1 ml) with 1% alcoholic *m*-dinitrobenzene (1 ml). A strong purple color developed within 10 min. Veracevine-D-orthoacetate triacetate (XXII) and its dehydro derivative (XXIII) gave no color when treated as above. (2) Furfural (0·1 ml) was added to a solution of the formamido ketone (10 mg) in alcohol (2 ml) and 15% sodium hydroxide solution (0·1 ml). After 30 min at room temp, the mixture was extracted with chloroform and the chloroform solution was washed with dilute sodium bisulfite solution and water and evaporated to dryness at reduced pressure giving a yellow amorphous residue, λ_{max} 318 mμ, attributable to a furfurylidene grouping.[17] Treatment of XXII in a similar manner afforded an amorphous product with no significant absorption in the ultraviolet.

(b) *From dehydroveracevine-*D-*orthoacetate triacetate.* A solution of the dehydro compound (XXIII, 350 mg), 277–279° dec. was added to the complex from chromium trioxide (700 mg) and pyridine (15 ml), and the mixture was treated as in the previous experiment. The formamido ketone (XXIV) obtained by crystallization from acetone–petroleum-ether (b.p. 40–60°), amounted to 140 mg, m.p. 262–264° dec.

Formamido ketone (XXX) *derived from cevine-*D-*orthoacetate triacetate*

(a) *From cevine-*D-*orthoacetate triacetate.* Cevine-D-orthoacetate triacetate[28] (18 g), m.p. 300–303° dec. in pyridine (100 ml) was added to the complex from chromium trioxide (36 g) and pyridine (250 ml), and the mixture was treated as in the previous experiment. The formamido ketone (XXX) crystallized from acetone–petroleum-ether (b.p. 40–60°) in the form of clusters of prismatic needles (1·21 g), m.p. 286–288° dec. Recrystallization from benzene afforded prismatic plates, (1·09 g), m.p. 287–288° dec. $[\alpha]_D^{25}$ +52° (*c*, 2·00, py.); λ_{max} 6·07 μ. (Found: C, 60·98; H, 7·08. Calcd. for $C_{35}H_{47}O_{13}N$: C, 60·94; H, 6·87%).

In a volatile acid determination[29] 30·00 mg of the formamido ketone yielded an amount of acid equivalent to 26·01 ml of 0·007547 N sodium thiosulfate; calculated for four mole-equivalents of acetic acid and one mole-equivalent of formic acid, as expected for structure XXX, 28·82 ml. The compound gave a strong positive test for active methylene group reactivity in the Zimmermann test.

The semicarbazone, prepared by treatment of XXX in dilute ethanol with semicarbazide hydrochloride and sodium acetate at room temp, crystallized from the reaction mixture on concentration under a stream of air. Recrystallization from aqueous ethanol afforded colorless needles, m.p. 273–274° dec. (Found: C, 57·91; H, 6·80; N, 6·93. Calcd. for $C_{36}H_{50}O_{13}N_4$: C, 57·90; H, 6·75; N, 6·93%).

(b) *From dehydrocevine-*D-*orthoacetate triacetate.* Oxidation of dehydrocevine-D-othoacetate (9·4 g), m.p. 256–257° dec. in pyridine (80 ml) with the complex from chromium trioxide (19 g) and pyridine (120 ml) as above afforded 7·0 g of twice recrystallized formamido ketone XXX, m.p. 287–288° dec.

*Alkaline hydrolysis of the formamido ketone derived from cevine-*D-*orthoacetate triacetate*

To a solution of the formamido ketone XXX (5 g), m.p. 286–288° dec. in methanol (40 ml) was added 20% sodium hydroxide solution (5 ml) and the mixture was allowed to stand at room temp overnight. Water (25 ml) was added and the solution was extracted with chloroform. The chloroform extract was washed with water (10 ml) and the residue obtained on evaporation at reduced pressure was crystallized from acetone. Recrystallization from acetone gave colorless needles (2·3 g) m.p. 259–260° dec. $[\alpha]_D^{25}$ +22° (*c*, 2·00, py.); λ_{max} 5·85 μ, 6·07 μ. (Found: C, 61·66; H, 7·24. Calcd for $C_{29}H_{41}O_{10}N$: C, 61·80; H, 7·34%).

Formamido ketone (XXXIII) *derived from cevagenine-*C-*orthoacetate diacetate*

Cevagenine-C-orthoacetate diacetate[14] (18 g), m.p. 283–285° dec. in pyridine (100 ml) was added to the complex from chromium trioxide (36 g) and pyridine (250 ml), and the mixture was treated as described above for XXIV. Crystallization of the crude product from acetone–petroleum ether (b.p. 40–60°) gave prisms (4·0 g), m.p. 252–254° dec. A further recrystallization from 95% ethanol

[29] J. R. Dyer in David Glick, *Methods of Biochemical Analysis* Vol. III, p. 131. Interscience, New York (1956).

VOL. 7 1959

gave colorless prisms (2·5 g), m.p. 253–255° dec. $[\alpha]_D^{27}$ −83° (*c*, 2·26, diox.). (Found: C, 60·96; H, 7·10. Calcd. for $C_{33}H_{43}O_{12}N$: C, 61·17; H, 7·00%).

In a volatile acid determination[29] 22·23 mg of product yielded an amount of acid equivalent to 13·75 ml of 0·009675 N sodium thiosulfate; calculated for three mole-equivalents of acetic acid and one mole-equivalent of formic acid, as expected for structure XXXIII, 14·19 ml.

Lithium aluminum hydride reduction was effected as follows. The formamido ketone (500 mg), m.p. 253–255° dec. in tetrahydrofuran (25 ml) was treated with lithium aluminum hydride (1 g) in tetrahydrofuran (50 ml) and the mixture was shaken for 15 min. The solution was then heated under reflux for 4 hr. After cooling in ice, water (2·7 ml) was added cautiously. Chloroform (50 ml) was added and the mixture was shaken and passed through Filtercel. The filter cake was washed with chloroform (150 ml) and the combined chloroform extracts were washed with water (15 ml) and evapoated under reduced pressure. The amorphous residue was purified by fractional precipitation from ether with petroleum ether (b.p. 40–60°) and rejection of precipitated colored solid until the filtrate was colorless. Evaporation to dryness afforded a colorless amorphous solid, m.p. 140–210°, λ_{max} 2·85–3·00 μ (OH). The infrared spectrum showed no significant absorption in the 5·75–6·10 μ (C=O) region. (Found: N-methyl, 2·38. Calcd. for $C_{29}H_{43}O_9N$: N-methyl, 2·75%).

Veracevine-D-dihydroorthoacetate triacetate (XXV)

(a) *From dehydroveracevine-D-orthoacetate triacetate.* Dehydroveracevine-D-orthoacetate triacetate (XXIII, 500 mg), m.p. 277–279° dec. in acetic acid (25 ml) and conc HCl (0·1 ml) was hydrogenated over platinum oxide (100 mg) at room temp and atmospheric pressure. In 2¼ hr two mole-equivalents of hydrogen was absorbed and hydrogen uptake ceased. The reaction mixture was filtered, diluted with water, adjusted with ammonium hydroxide to pH 9 and extracted with chloroform. The residue obtained on evaporation of the chloroform was crystallized from ether to yield needles (310 mg), m.p. 299–300° dec. $[\alpha]_D^{25}$ −21° (*c*, 2·09, diox.). (Found: C, 63·53; H, 7·85; acetyl, 19·98. Calcd. for $C_{35}H_{51}O_{11}N$: C, 63·52; H, 7·77; acetyl, 19·53%).

(b) *From veracevine-D-orthoacetate triacetate.* Hydrogenation of veracevine-D-orthoacetate triacetate (150 mg), m.p. 254–256° dec. in acetic acid (15 ml) and conc HCl (0·1 ml) with platinum oxide (30 ml) as described above resulted in uptake of one mole-equivalent of hydrogen in 1 hr. Isolation as described above afforded veracevine-D-dihydroorthoacetate triacetate (105 mg) in the form of colorless needles, m.p. 299–300° dec. undepressed on admixture with authentic XXV obtained as above. The infrared spectra of the two samples were identical.

Dehydrocevine triacetate

Cevine triacetate[18] (1·5 g), m.p. 303–304° dec. in chloroform (50 ml) was treated with N-bromosuccinimide (0·6 g) in chloroform (60 ml) and the mixture was allowed to stand at room temp for 30 min. The product was treated as described above for XXIII and the residue from chloroform was crystallized from water–acetone–methanol to give 816 mg, m.p. 234–239° dec. Partial purification was effected by dissolving this material in dil HCl, adding excess sodium acetate, and extracting the mixture with ether. The residue obtained on evaporation of the ether was crystallized from aqueous acetone to give 390 mg, m.p. 255–260° dec. This product was dissolved in benzene and chromatographed on Merck acid-washed alumina (10 g), using benzene, benzene–chloroform (50 : 50) and chloroform as eluants. The residues obtained from the benzene–chloroform and chloroform fractions were combined and crystallized from aqueous acetone to yield 135 mg, m.p. 292–294° dec. Recrystallization from the same solvents gave colorless needles, m.p. 294–295° dec. $[\alpha]_D^{25}$ +5° (*c*, 2·00, py.) The ultraviolet spectrum exhibited no maximum other than end-absorption. (Found: C, 60·98; H, 7·31. Calcd. for $C_{33}H_{47}O_{11}N \cdot H_2O$: C, 60·89; H, 7·59%).

Catalytic hydrogenation of dehydrocevine triacetate

Dehydrocevine triacetate (250 mg), m.p. 293–295° dec. in acetic acid (20 ml) and conc HCl (0·1 ml) was hydrogenated over 50 mg of platinum oxide at room temp and atmospheric pressure. Uptake of hydrogen ceased after one mole-equivalent had been absorbed. Treatment as described above for XXV gave a crude product which crystallized from benzene–ether in the form of colorless needles (218 mg), m.p. 304–305° dec. undepressed on admixture with an authentic sample of cevine triacetate. The infrared spectra of the two samples were identical.

Formamido ketone derived from cevine triacetate

(a) *From cevine triacetate.* Chromium trioxide–pyridine oxidation of cevine triacetate (5 g), m.p. 303–304° dec. by the procedure described above for XXIV afforded a crude product which was crystallized from acetone to give 1·04 g of product. Recrystallization from acetone gave colorless prismatic plates (774 mg), m.p. 210–220° dec. after sintering from 162°; $[\alpha]_D^{27}$ −31° (*c*, 2·16, diox.). (Found: C, 59·81; H, 7·49. Calcd. for $C_{23}H_{37}O_{13}N\cdot(CH_3)_2CO$: C, 59·70; H, 7·38%).

(b) *From dehydrocevine triacetate.* Chromium trioxide–pyridine oxidation of dehydrocevine triacetate (250 mg), m.p. 293–295° dec. as described above gave 85 mg of formamido ketone, m.p. 210–220° dec. undepressed on admixture with the specimen described above under part (a). The infrared spectra of the two specimens were identical.

VOL.
7
1959

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STUDIES ON THE STEROIDAL COMPONENTS OF DOMESTIC PLANTS—XIX[1]

THE STRUCTURE OF KOGAGENIN, A SAPOGENIN FROM *DIOSCOREA TOKORO*, MAKINO[2]

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Abstract—The structure of kogagenin, a steroidal sapogenin isolated from the epigeous part of *Dioscorea tokoro*, Makino, has been shown to be 25D-spirostane-1β,2β,3α,5β-tetrol. This sapogenin is the first example of a naturally occurring spirostane tetrol.

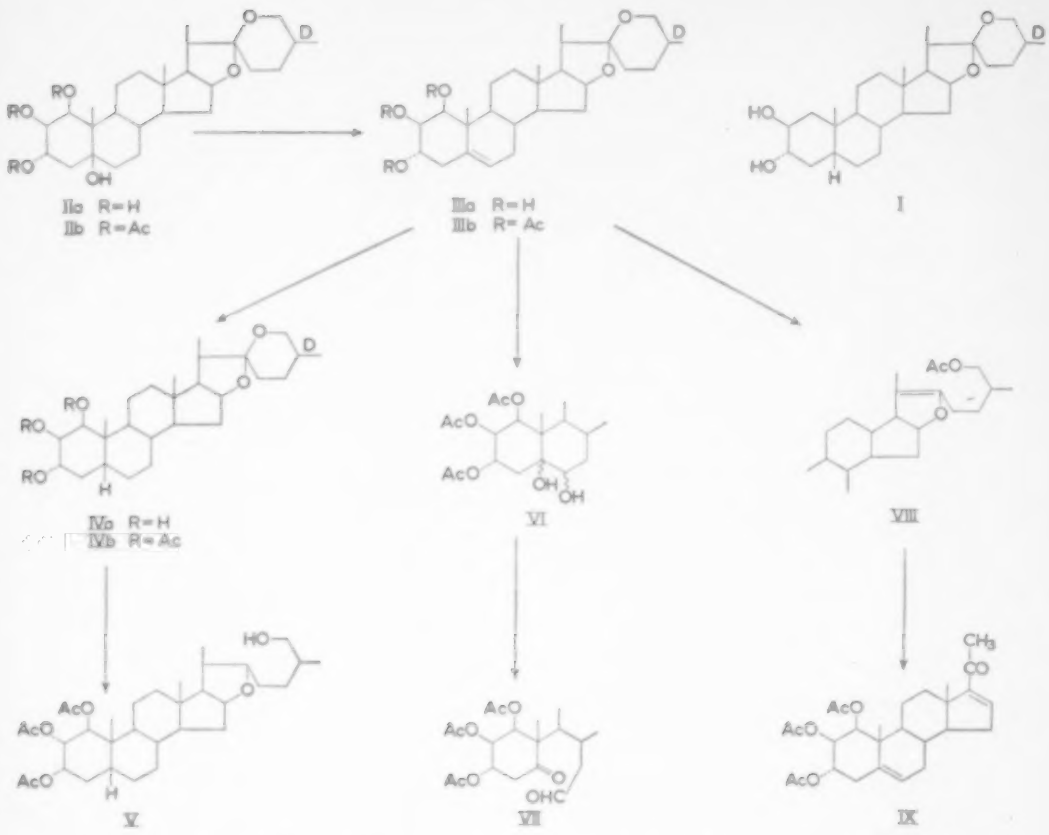
RECENTLY, we isolated two new sapogenins, yonogenin and kogagenin,[3,4] together with the known tokorogenin[5,6] from the epigeous part of *Dioscorea tokoro*, Makino. The structure of yonogenin was established as 25D,5β-spirostane-2β,3α-diol (I), and this sapogenin is the first example of a 3α-hydroxylated sapogenin from a plant source. After publication of the outline of the above results, the structure of tokorogenin was clarified as 25D,5β-spirostane-1β,2β,3α-triol (IVa), that is 1β-hydroxyyonogenin, by Morita.[6]

The elucidation of the structure of kogagenin, an uncharacterized sapogenin of this plant, is the subject of the present paper.

Kogagenin, $C_{27}H_{44}O_6$, $[\alpha]_D$ $-27°$ (pyridine), melts at 318–322° (dec.) and gives a triacetate (IIb). The infra-red spectrum of this sapogenin shows neither a ketonic band nor an isolated double bond but hydroxyl group absorption. Comparison of the intensities of the characteristic absorption bands at 10·90 μ and 11·10 μ[7] shows that kogagenin is a 25D (iso) sapogenin. As the triacetate (IIb) still shows a hydroxyl absorption band in the infra-red spectrum, this sapogenin is assumed to be a 25D-tetrahydroxyspirostane. Kogagenin afforded an acetonide (XII). The triacetate (IIb) was not affected by chromium trioxide–pyridine oxidation and was very easily dehydrated to an anhydro derivative, $C_{33}H_{48}O_8$, (IIIb), with thionyl chloride and pyridine. Thus kogagenin has one *cis*-α-glycol (or less likely, a diaxial 1,3-glycol) group and a tertiary hydroxyl function.

The catalytic hydrogenation of the above-mentioned anhydrokogagenin triacetate (IIIb) gave important evidence for the structural elucidation of this sapogenin. Thus when the IIIb was hydrogenated catalytically with platinum oxide in acetic acid it gave two saturated compounds. One of them, having a melting point of 253–255°, was identical in all respects with tokorogenin triacetate (IVb). Based on the analytical

[1] Part XVIII; Ken'ichi Takeda and Tokuo Kubota, *Chem. Pharm. Bull.* **6**, 536 (1958).
[2] An outline of this paper was presented at the Symposium on *Organic Natural Products* of the Chemical Society of Japan in Osaka, Oct. 18 (1958).
[3] K. Takeda, T. Okanishi and A. Shimaoka, *Yakugaku Zassi* **77**, 822 (1957).
[4] K. Takeda, T. Okanishi and A. Shimaoka, *Chem. Pharm. Bull.* **6**, 532 (1958).
[5] M. Nishikawa, K. Morita, H. Hagiwara and M. Inoue, *Yakugaku Zassi* **74**, 1165 (1954).
[6] K. Morita, *Pharm. Bull.* **5**, 494 (1957).
[7] M. E. Wall, C. R. Eddy, M. L. McClennen and M. E. Klumpp, *Analyt. Chem.* **24**, 1337 (1952); R. N. Jones, E. Katzenellenbogen and K. Dobriner, *J. Amer. Chem. Soc.* **75**, 158 (1953).



values and the infra-red spectrum it is suggested that the structure of the other saturated compound, m.p. 167–169°, is that of dihydrotokorogenin triacetate where ring F is opened by catalytic reduction. This has now been proved by direct comparison with dihydrotokorogenin triacetate (V) which was prepared from tokorogenin acetate by the method of Marker *et al.*[8] We could not detect any isomer among the reduction products other than tokorogenin triacetate and its dihydro derivative. From these results the constitution of kogagenin is now established as x-hydroxytokorogenin.

In order to determine the position of the fourth, tertiary hydroxyl group, the location of the double bond in anhydrokogagenin acetate (IIIb) was examined. The possibility of the double bond being at C-7, C-8 or C-8(14) was excluded since the hydrogenation of IIIb with platinum oxide in acetic acid proceeded smoothly without migration of the double bond.[9] Osmium tetroxide oxidation of IIIb followed by cleavage of the resulting diol (VI) with lead tetracetate gave an amorphous product, which not only showed an absorption band at 5·85 μ due to the six-membered ring ketone in the infra-red spectrum but also indicated the presence of an aldehyde

[8] R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, P. J. Goldsmith and C. H. Ruof, *J. Amer. Chem. Soc.* **69**, 2167 (1947).
[9] L. F. Fieser and M. Fieser, *Natural Products related to Phenanthrene* (3rd Ed.) p. 240 (1949).

function by the positive triphenyltetrazolium test. From this observation the position of the double bond in III is limited to Δ^5 (or Δ^4) or Δ^{14}.

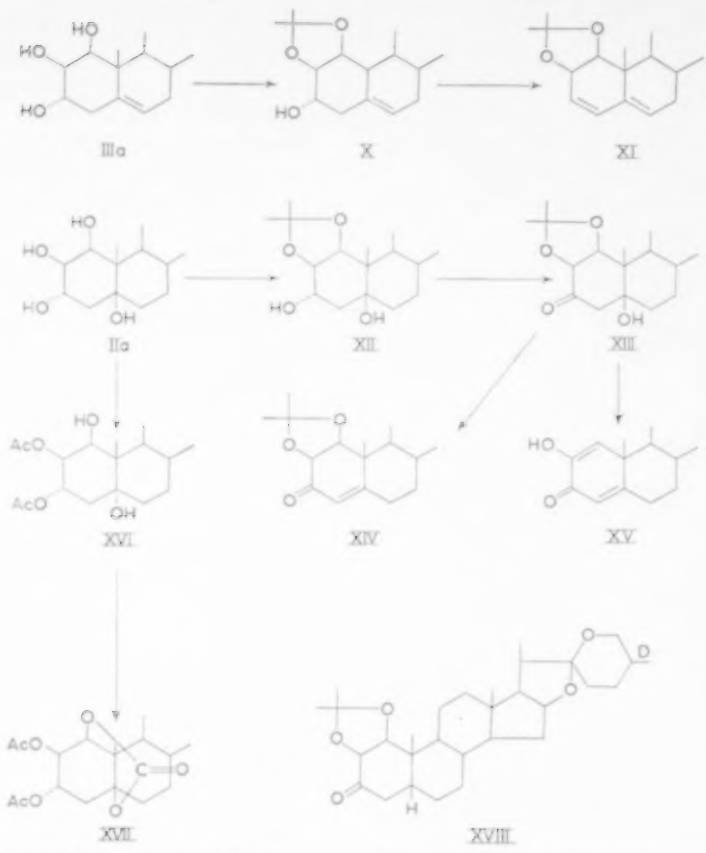
If the double bond in IIIb were located at C-14, the corresponding pregnene derivative (IX) of anhydrokogagenin would now be a $\Delta^{14,16}$-dien-20-one which should exhibit typical ultra-violet absorption at 307–309 mμ[10]. A Δ^{16}-pregnene derivative (IX), was obtained from anhydrokogagenin *via* the *pseudo*sapogenin (VIII) followed by the oxidation. This Δ^{16}-pregnene derivative showed an ultra-violet absorption at 239 mμ ($\log \varepsilon = 4{\cdot}00$) thus establishing the presence of Δ^{16}-20-ketone group[10] without additional conjugation.

The remaining position, C-5, for the tertiary hydroxyl group was proved by the following methods. Attempts to obtain a Δ^4-3-keto derivative of kogagenin by oxidation of anhydrokogagenin acetonide (X) with chromium trioxide–pyridine, chromium trioxide–acetone–sulphuric acid or by the Oppenauer oxidation were all unsuccessful, and in all cases the starting material was recovered almost quantitatively. When anhydrokogagenin (IIIa) was treated with acetone and *p*-toluenesulphonic acid in order to synthesize the acetonide (X), a small amount of by-product (XI) was obtained and this showed an ultra-violet maximum at 236 mμ ($\log \varepsilon = 4{\cdot}31$) in keeping with the chromophore of the $\Delta^{3,5}$-diene system. The dehydration of the above acetonide (X) with phosphorus oxychloride in pyridine also gave the same diene (XI) but the yield was very poor. These findings support the fact that the position of the fourth tertiary hydroxyl group is at C-5.

Anhydrokogagenin triacetate (IIIb) was saponified by methanolic potassium hydroxide to the free triol (IIIa), m.p. 240–243°, which does not contain an allylic hydroxyl function since this triol does not show any colouration by the Rosenheim test.[11] Acetylation of IIIa regenerated IIIb. It appeared reasonable, therefore, that the position of the double bond in anhydrokogagenin is at 5-6 rather than at 4-5. The fact that the hydrogenation of anhydrokogagenin acetate yielded only the normal (5β) steroid agrees with the results of the reduction of 3α-acetoxy-Δ^5-steroids.[12]

Finally, we obtained the Δ^4-3-keto derivative by the direct oxidation of kogagenin acetonide (XII). Chromium trioxide–pyridine oxidation of kogagenin acetonide gave a ketone (XIII), but its infra-red spectrum showed the weak absorption bands at 5·96 μ and 6·16 μ corresponding to a Δ^4-3-ketone group, besides the absorption bands at 2·84 μ (hydroxyl) and 5·76 μ (ketone). The ultra-violet absorption spectrum also showed absorption at 246 mμ ($\varepsilon = 1670$), indicating that this ketone was contaminated by ca. 10 per cent of the Δ^4-3-keto derivative (XIV). Attempts to purify XIII without dehydration of the C-5 tertiary hydroxyl group were unsuccessful. The crude ketone was easily dehydrated by silica gel chromatography and afforded the Δ^4-3-keto acetonide (XIV) in a pure state. Treatment of XIII with potassium hydroxide in aqueous methanol at room temperature in order to obtain XIV gave a different compound, having an empirical formula $C_{27}H_{38}O_4$, m.p. 224–227°. The analytical values suggest the elimination of one mole of acetone with the loss of one mole of water from the starting material during the reaction. The postulated constitution XV for this compound was in good agreement with the following facts: (a) XV gave a quinoxaline derivative, m.p. 283–284°, with *o*-phenylenediamine;

[10] L. Dorfman, *Chem. Rev.* **53**, 47 (1953).
[11] R. Schoenheimer and E. A. Evans, Jr., *J. Biol. Chem.* **114**, 567 (1936).
[12] J. R. Lewis and C. W. Shoppee, *J. Chem. Soc.* 1365 (1955).



(b) the infra-red spectrum of this compound showed absorption bands at 2·96 μ (hydroxyl) and at 6·09 and 6·17 μ (conjugated unsaturated ketone) and the ultra-violet absorption maximum appeared at 254 mμ (log $\varepsilon = 4{\cdot}13$) with a small shoulder at 290 mμ.[13]

Consequently, kogagenin can now be defined as 25D-spirostane-1β,2β,3α,5ξ-tetrol and there remains only the determination of the configuration of the C-5 hydroxyl group for the complete elucidation of the structure. Closely related to kogagenin in *Dioscorea tokoro* are yonogenin (I) and tokorogenin (IVa), and it seems likely that kogagenin should have the same *cis* configuration of the A/B ring juncture as the other two. This assumption was supported by the fact that the rotatory dispersion curve[14] of the above-mentioned 3-ketone (XIII) closely resembles that of XVIII derived from tokorogenin acetonide (Fig. 1). The rotatory dispersion curves of other 5β-hydroxy-3-keto steroids also support our conclusion.[15]

[13] J. S. Baran, *J. Amer. Chem. Soc.* **80**, 1687 (1958).

[14] Rotatory dispersion curves were measured by Mrs. T. Nakano at Wayne State University through the kind offices of Dr. Carl Djerassi. The sample of XIII contained 12% of the Δ^4-3-ketone (XIV); however, by comparison with the curve of the pure Δ^4-3-ketone (XIV) it was confirmed that the Δ^4-3-ketone contaminant practically did not affect the rotatory dispersion curve of XIII. Rotatory dispersion curves of authentic Δ^4-3-keto and 5β-3-keto steroids can be found in the review article of C. Djerassi, *Bull. Soc. Chem. Fr.* 741 (1957).

[15] Private communication of Dr. C. Djerassi.

More convincing evidence for the A/B ring *cis*-fusion was achieved by experiments described below. Kogagenin acetonide (XII) did not condense with phosgene under the usual conditions, thus indicating the lack of a 3α,5α-glycol grouping. On the other hand, it was now found that the acetylation of kogagenin under mild conditions gave in excellent yield the corresponding diacetate (XVI). It can be assumed that orientation of these two hydroxyl groups is equatorial from the ease of acetylation and this requires the A/B ring *cis* juncture with the 5β-hydroxyl group. On the basis of these observations, the above diacetate (XVI) should be 25D-spirostane-1β,2β,3α,-5β-tetrol 2,3-diacetate and this could be condensed with phosgene to yield a

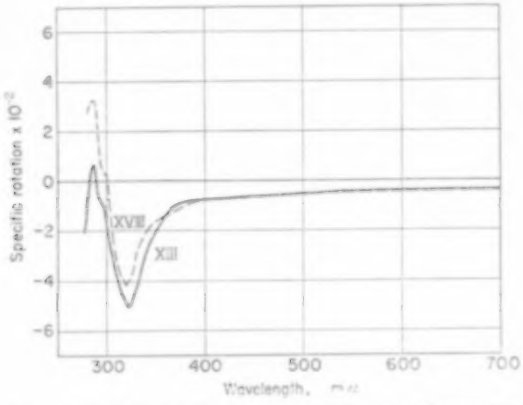


FIG. 1. Optical rotary dispersion curves (dioxane solution) of 25D-spirostane-1β-2β,5β-triol-3-one 1,2-acetonide (XIII) and 25D,5β-spirostane-1β,2β-diol-3-one acetonide (XVIII).

1β,5β-carbonyldioxy derivative (XVII), as expected. It seems appropriate, therefore, to conclude that the hydroxyl group at C-5 in kogagenin is β-oriented and this sapogenin is described as 25D-spirostane-1β,2β,3α,5β-tetrol (IIa). Kogagenin is the first example of a naturally occurring spirostane tetrol.

Thus, the structures of the four sapogenins isolated until now from *Dioscorea tokoro* have been made clear. Yonogenin, tokorogenin and kogagenin are respectively dihydroxy-, trihydroxy- and tetrahydroxy-sapogenins, and at the same time all 3α-hydroxylated sapogenins, while the remaining one, diosgenin, is a 3β-hydroxylated sapogenin. It is of further interest to note that kogagenin has not been isolated from the rhizome of this plant,[16] while diogenin has not been isolated from the epigeous part of the plant. Also, according to Morita,[17] quantitative analysis of sapogenins in the rhizome of *Dioscorea tokoro* showed that this plant could be divided into two varieties; in one variety the sapogenin component being mainly yonogenin and tokorogenin, while in the other being diosgenin.

It should be noted, however, that the biogenetic relationship between 3α-hydroxylated sapogenins and 3β-hydroxylated sapogenins, and the reason for the particular location of diosgenin and kogagenin in plant material is unknown.

[16] M. Yamagishi and I. Nakamura, *Chem. Pharm. Bull.* **6**, 421 (1958).
[17] K. Morita, Abstract of the Symposium on *Organic Natural Products* of the Chemical Society of Japan, p. 101, (1958).

EXPERIMENTAL

All melting points are uncorrected. Ultra-violet absorption spectra were measured in 95% ethanolic solutions with a Beckman DU spectrophotometer. Infra-red spectra were determined with a Perkin–Elmer single-beam instrument, Model 12C, in Nujol mull (unless otherwise stated).

Kogagenin triacetate (IIb). A mixture of kogagenin (600 mg), acetic anhydride (6 ml) and pyridine (3 ml) was refluxed for 2 hr. The product, isolated with benzene in the usual manner, was recrystallized from methanol to give IIb, m.p. 249–252°, $[\alpha]_D$ −26° (*c* 1·0, chloroform). (Found: C, 67·09; H, 8·50. $C_{33}H_{50}O_9$ requires: C, 67·09; H, 8·53%).

Kogagenin acetonide (XII). A mixture of kogagenin (500 mg), acetone (500 ml), benzene (200 ml) and *p*-toluenesulphonic acid (500 mg) was heated under reflux for 22 hr. After neutralizing with sodium bicarbonate, the solution was concentrated under reduced pressure and extracted with benzene. The extract was washed with water, dried and evaporated. The resulting crystalline residue was chromatographed on alumina (15 g), and elution with benzene–chloroform (1 : 1) and with chloroform furnished crude acetonide (316 mg), which was recrystallized from chloroform–methanol to give prisms (260 mg), m.p. 273–275°, $[\alpha]_D$ −23° (*c* 1·15, chloroform). (Found: C, 71·59; H, 9·75. $C_{30}H_{48}O_6$ requires: C, 71·39; H, 9·59%).

The chloroform–methanol (1 : 1) eluate from the above chromatogram gave unchanged kogagenin (230 mg).

Dehydration of kogagenin triacetate (IIb). The triacetate (500 mg) was dissolved in pyridine (5 ml), cooled to 0° and a mixture of thionyl chloride (0·50 g) in pyridine (2 ml) was added dropwise. After 1 hr at 0°, ice was added to the mixture and the product was extracted with ether. The extract was washed with dilute HCl, sodium bicarbonate solution and water, dried and evaporated leaving an oil (490 mg). Crystallization from methanol gave scales (395 mg) of *anhydrokogagenin triacetate* (IIIb), m.p. 171–173°, $[\alpha]_D$ +33° (*c* 1·0, chloroform). (Found: C, 69·05; H, 8·61. $C_{33}H_{48}O_8$ requires: C, 69·20; H, 8·45%).

IIIb (500 mg) was saponified by refluxing for 1 hr with 1·5% methanolic KOH solution (20 ml). The cooled reaction mixture was diluted with water, and the precipitate was filtered and recrystallized from methanol to give *anhydrokogagenin* (IIIa) as needles, m.p. 240–243°, $[\alpha]_D$ −70° (*c* 1·0, chloroform), negative Rosenheim test. (Found: C, 72·64; H, 9·41. $C_{27}H_{42}O_5$ requires: C, 72·61; H, 9·48%)

Catalytic reduction of IIIb. A solution of IIIb (100 mg) in glacial acetic acid (7 ml) was shaken with pre-reduced platinum oxide (100 mg) in an atmosphere of hydrogen. The absorption of hydrogen was rapid and 1·5 equivalent was taken up within 30 min when hydrogenation was stopped. The catalyst was filtered, the solvent was removed *in vacuo* and the crystalline residue was recrystallized from methanol to yield tokorogenin acetate (IVb) as prisms (45 mg), m.p. 253–255°, $[\alpha]_D$ −20° (*c* 1·0, chloroform). Identity with an authentic sample was confirmed by a mixed melting point determination and infra-red comparison. (Found: C, 69·27; H, 8·98. Calc. for $C_{33}H_{50}O_8$: C, 68·96; H, 8·77%).

Saponification of IVb with 3% methanolic KOH and recrystallization from methanol gave needles of tokorogenin, m.p. 266–268°, which was identical with an authentic sample.

After concentrating the mother liquor of the above acetate, the residue was chromatographed on alumina (3 g). Elution with petroleum ether–benzene (1 : 1) afforded an additional 5 mg of IVb, while elution with benzene and with benzene–ether (19 : 1) yielded *dihydrotokorogenin triacetate* (V) (35 mg), which was recrystallized from methanol giving needles, m.p. 167–169°, $[\alpha]_D$ +40° (*c* 1·0, chloroform). Identity with the specimen (described below) prepared from authentic tokorogenin acetate was established by a mixed m.p. and the respective infra-red spectra. (Found: C, 68·77; H, 9·30. $C_{33}H_{52}O_8$ requires: C, 68·72; H, 9·09%).

Dihydrotokorogenin triacetate (V, *furostane-1β,2β,3α,26-tetrol 1β,2β,3α-triacetate*). IVb (50 mg) in glacial acetic acid (6 ml) was shaken with Adams' catalyst (50 mg) in an atmosphere of hydrogen for 4·5 hr at 70–80°. The catalyst was filtered, the solvent removed *in vacuo* and the product recrystallized from methanol, m.p. 167–169°, $[\alpha]_D$ +37° (*c* 0·65, chloroform), λ_{max}^{Nujol} 2·83 μ (hydroxyl band) but no spiroketal bands at 10·19, 10·90, 11·10 and 11·58 μ. (Found: C, 68·38; H, 9·17. $C_{33}H_{52}O_8$ requires: C, 68·72; H, 9·09%).

Treatment of IIIb *with osmium tetroxide*. Osmium tetroxide (350 mg) in benzene (10 ml) was added to a solution of IIIb (300 mg) in pyridine (5 ml) and stored in the dark for 53 hr at room temp. The mixture was saturated with hydrogen sulphide, the precipitate was filtered and the filtrate

evaporated to dryness *in vacuo*. Crystallization from ethanol yielded the *triacetate-diol* (VI) (150 mg), m.p. 252–254°, $[\alpha]_D$ −44° (*c* 1·0, chloroform). (Found: C, 65·34; H, 8·40. $C_{33}H_{50}O_{10}$ requires: C, 65·32; H, 8·31%).

To a solution of VI (100 mg) in glacial acetic acid (10 ml) lead tetraacetate (0·7 g) in glacial acetic acid (20 ml) was added. After standing overnight at room temp, the mixture was diluted with water (60 ml) and extracted with ether. The extract was washed with 10% sodium carbonate solution and water, dried and evaporated. Attempts to crystallize the resulting gum were unsuccessful. This product gave a positive triphenyltetrazolium test and showed a strong infra-red ketonic band at 5·85 μ.

Degradation of anhydrokogagenin acetate (IIIb) *to* $\Delta^{5,16}$*-pregnadien-1β,2β,3α-triol-20-one triacetate* (IX). IIIb (450 mg) in pyridine (2 ml) and acetic anhydride (2 ml) was heated under reflux with ethylamine hydrochloride (0·3 g) for 5·5 hr. The cooled reaction mixture was poured on crushed ice and the product was extracted with ether. Chromium trioxide (0·3 g) in 80% acetic acid (3 ml) was added dropwise to a solution of the furosten (VIII) in acetic acid (9 ml). After stirring for 2 hr at room temp, the mixture was diluted with water and extracted with ether. The ether solution was washed with sodium carbonate solution and water and evaporated leaving a gummy solid which was saponified with 1% ethanolic KOH. After re-acetylation with acetic anhydride–pyridine (refluxing), the product was purified by chromatography, followed by recrystallization from aqueous ethanol; yield 95 mg, m.p. 150–152°, $[\alpha]_D$ +168° (*c* 1·0, chloroform), λ_{max}^{EtOH} 239 mμ, log ε 4·00. (Found: C, 68·45, H, 7·65. $C_{27}H_{36}O_7$ requires: C, 68·62; H, 7·68%).

Δ^5-25D-*Spirostene-1β,2β,3α-triol* 1,2-*acetonide* (X) *and by-product* (XI) *from the anhydro-triol* (IIIa). IIIa (160 mg) was refluxed for 6 hr in acetone (30 ml) containing *p*-toluenesulphonic acid (10 mg). The solution was neutralized with sodium bicarbonate solution and concentrated under reduced pressure. The product was extracted with ether and the extract washed with water and dried. After removal of the solvent, the crystalline residue was chromatographed on alumina. The fractions (7 mg), m.p. 157–161°, eluted with petroleum ether–benzene (9 : 1) yielded the diene-acetonide (XI) (see below). The next fractions, eluted with petroleum ether–benzene (4 : 1 to 1 : 1), on recrystallization from methanol furnished the acetonide (X) (93 mg), m.p. 208–210°, $[\alpha]_D$ −61° (*c* 1·0, chloroform). (Found: C, 74·26; H, 9·51. $C_{30}H_{46}O_5$ requires: C, 74·07; H, 9·46%).

The diene-acetonide (XI) on crystallization from methanol showed m.p. 162–164°, $[\alpha]_D$ −115° (*c* 1·0, chloroform), λ_{max}^{EtOH} 236 mμ, log ε 4·31. (Found: C, 76·82; H, 9·65. $C_{30}H_{44}O_4$ requires: C, 76·88; H, 9·46%).

Dehydration of Δ^5-25D-*spirostene-1β,2β,3α-triol* 1,2-*acetonide* (X). A mixture of the Δ^5-en-3-ol (X) (80 mg), pyridine (4 ml) and phosphorus oxychloride (0·5 g) was heated (steam bath) for 45 min. The solution was poured on crushed ice and extracted with ether. The extract was washed with dilute HCl, sodium bicarbonate solution and water, dried and evaporated yielding an oily residue (50 mg). Crystallization from methanol gave needles (15 mg), m.p. 150–154°, identical with a sample of the diene (XI), by-product in acetonization described above, by admixture and infra-red comparison.

Attempted oxidation of X. The Δ^5-en-3-ol (X) was recovered unchanged after treatment with the chromium trioxide–pyridine complex for 20 hr at 37° or with chromium trioxide–sulphuric acid–acetone solution for 10 min at 15°, and it was not oxidized by refluxing for 6 hr with aluminium isopropoxide and cyclohexanone in toluene.

Oxidation of kogagenin acetonide (XII). XII (120 mg) in pyridine (3 ml) was added at 0° to the complex prepared from chromium trioxide (150 mg) and pyridine (1·5 ml) and the mixture was allowed to stand at room temp for 16 hr. The product was extracted with ether and crystallized from methanol to give the crude ketone (XIII) as needles, m.p. 189–191° (dec.). The structure of XIII was supported by the infra-red spectrum having strong bands at 2·84 and 5·76 μ, but the co-existence of a small amount of the α,β-unsaturated ketone (XIV) was also indicated by bands at 5·93 and 6·16 μ. This was also shown by the ultra-violet absorption at 246 mμ (ε 1,670). This sample was used for the determination of the rotatory dispersion curve (Fig. 1), since further recrystallization brought no alteration in this ultra-violet spectrum.

A solution of the crude ketone above (80 mg) in petroleum ether–benzene (1 : 1) was absorbed on a silica gel column. Elution with benzene and with benzene–chloroform (9 : 1) and recrystallization of the eluate from acetone–hexane furnished Δ^4-25D-*spirostene-1β,2β-diol-3-one acetonide* (XIV) (54 mg) as needles, m.p. 193–198°, λ_{max}^{EtOH} 246 mμ, log ε 4·10. Further recrystallization from methanol

gave the analytical sample with the following constants: m.p. 197–200°, $[\alpha]_D$ −100° (*c* 1·0, chloroform), λ_{max}^{EtOH} 246 mμ, log ε 4·15: λ_{max}^{Nujol} 5·93 and 6·16 μ, no hydroxyl absorption. (Found: C, 74·74; H, 9·04. $C_{30}H_{44}O_5$ requires: C, 74·34; H, 9·15%).

To the crude ketone above (20 mg) in methanol (5 ml), was added 10% aqueous KOH (0·5 ml) and the mixture was kept at room temp overnight. The mixture was diluted with water, neutralized with dilute HCl and extracted with ether. The ether extract was washed with water, dried and evaporated. The crystalline residue (15 mg) was recrystallized from acetone giving leaflets of $\Delta^{1,4}$-25D-*spirostadien*-2-*ol*-3-*one* (XV) showing the following properties; m.p. 224–227°, $[\alpha]_D$ −102° (*c* 0·36, chloroform); λ_{max}^{Nujol} 2·96, 6·09 and 6·17 μ; λ_{max}^{EtOH} 254 mμ, log ε 4·13 with a weak shoulder at 290 mμ; reddish-purple colour with alcoholic ferric chloride solution. (Found: C, 75·81; H, 9·06. $C_{27}H_{38}O_4$ requires: C, 76·02; H, 8·98%).

Refluxing of $\Delta^{1,4}$-3-on-2-ol (XV) with *o*-phenylenediamine in ethanol gave a quinoxaline derivative, orange-yellow needles, m.p. 283–284°.

Kogagenin diacetate (XVI). Kogagenin (98 mg) was added to a mixture of chloroform (4 ml), acetic anhydride (1 ml) and pyridine (4 ml). On standing overnight at room temp, the sapogenin had dissolved completely. Water and ether were then added, the ether layer was washed with dilute HCl, sodium bicarbonate solution and water and evaporated to leave a crystalline residue (123 mg). Crystallization from chloroform–methanol gave scales of the diacetate (XVI) (87 mg), m.p. 275–277°, $[\alpha]_D$ −13° (*c* 1·1, chloroform). (Found: C, 67·79; H, 8·85. $C_{31}H_{48}O_8$ requires: C, 67·85; H, 8·82%).

Reaction of XVI *with phosgene*. XVI (80 mg) was dissolved in alcohol-free chloroform (6 ml), about 1 ml of the chloroform was removed by distillation and then pyridine (4 ml) was added. The mixture was cooled to −15° and a 10% phosgene–toluene solution (12 ml) added dropwise. The temperature of the reaction mixture was slowly raised to 15° during 1 hr and was maintained at 15–20° overnight. After destruction of the excess phosgene with ice, water and ether were added, and the ether layer was washed successively with dilute HCl, sodium bicarbonate solution and water, dried and evaporated. The gummy residue was chromatographed on alumina (2 g) and the benzene eluate (56 mg) was crystallized from acetone–hexane and then from methanol yielding prisms (37 mg) of 25D-*spirostane*-1β,2β,3α,5β-*tetrol* 1,5-*carbonate* 2,3-*diacetate* (XVII), m.p. 169–172°, $[\alpha]_D$ +27° (*c* 1·1, chloroform); $\lambda_{max}^{CS_2}$ 5·66, 5.72, 8·08, 8·19 and 8·40 μ, no hydroxyl band. (Found: C, 66·57; H, 8·35. $C_{32}H_{46}O_9$ requires: C, 66·87; H, 8·07%).

The 1 : 1 chloroform–methanol eluate (34 mg) of the above chromatography furnished, after recrystallization from methanol, crystals (15 mg) with m.p. 257–266° probably representing impure starting material.

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VOL. 7 1959

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ISOLATION AND STRUCTURE OF THE FLUORESCENT SUBSTANCES FORMED IN THE OXIDATIVE REACTION OF ADRENALINE AND NORADRENALINE WITH ETHYLENEDIAMINE

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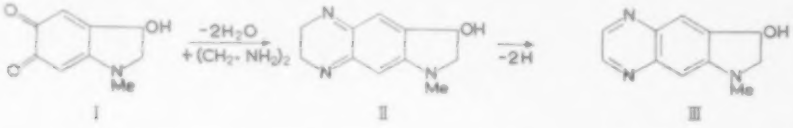
Abstract—One of the fluorescent products formed in the oxidative reaction of adrenaline with ethylenediamine has been characterized as 2,3-dihydro-3-hydroxy-l-methylpyrrolo-4,5-g quinoxaline (III). In the case of noradrenaline, the only fluorescent product found has been characterized as 1,2,3,4-tetrahydro-1,4,5,8-tetra-aza-anthracene (VII). The same tetrahydrotetra-aza-anthracene is also obtained from catechol, 2-methylnoradrenaline, adrenalone and 3,4-dihydroxymandelic acid. The chemistry and mechanism of formation of III and VII are discussed.

THE formation of a stable fluorescent compound by the reaction of adrenaline with ethylenediamine in the presence of air was demonstrated by Natelson *et al.*[1] Based on this reaction, a method for the determination of adrenaline and noradrenaline has been developed by Weil-Malherbe and Bone.[2] Further investigation by Burn and Field[3] has indicated that the reactions give rise to more than one product in each case, and an attempt to isolate these products and elucidate the chemistry involved seemed desirable.

The case of adrenaline was first examined. Weil-Malherbe and Bone had shown that the reaction proceeds via the formation of adrenochrome (I), and accordingly we oxidized adrenaline with silver oxide in methanol to adrenochrome and treated this solution with an excess of ethylenediamine. After dilution with water, extraction with ethyl acetate and concentration, chromatography on alumina gave a small (7 per cent), but easily reproducible, yield of a highly crystalline yellow material exhibiting an intense green fluorescence in solution. Elementary analysis indicated the formula $C_{11}H_{11}ON_3$, thus showing that the compound was formed from one mole each of adrenochrome and ethylenediamine with the loss of two moles of water and two hydrogen atoms. Moreover, the compound was optically active, showing that the secondary hydroxyl group was unaffected, and its u.v. spectrum (Fig. 1) resembled that of 7-aminoquinoxaline and showed a similar bathochromic shift on acidification.[4] It was therefore assigned the structure (—)-2,3-dihydro-3-hydroxy-l-methylpyrrolo-4,5-g-quinoxaline (III), and we suggest that it is formed via II as an intermediate. The same material was also obtained, though in lower yield, by the autoxidation of adrenaline in aqueous solution in the presence of ethylenediamine. In cold dilute mineral acids, the compound gives deep red non-fluorescent solutions, and is recovered unchanged on basification. However, if the acid solution is boiled

[1] S. Natelson, J. K. Lugovoy and J. B. Pincus, *Arch. Biochem. Biophys.* **23**, 157 (1949).
[2] H. Weil-Malherbe and A. D. Bone, *Biochem. J.* **51**, 311 (1952); **58**, 132 (1954); **67**, 65 (1957).
[3] G. P. Burn and E. O. Field, *Nature, Lond.* **178**, 542 (1956).
[4] A. R. Osborn, K. Schofield and L. N. Short, *J. Chem. Soc.* 4191 (1956).

for a few minutes and then basified, a less soluble dehydration product is obtained. This is the fully aromatic pyrrolo-quinoxaline (IX), and this dehydration can also be effected with acetic anhydride.

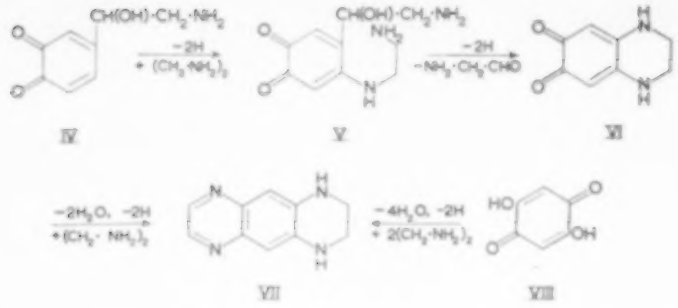


I II III

Run on paper (butanol–water), III has R_F of 0·69, identical with that of the fast-running green fluorescent spot described by Burn and Field. These authors also showed that a butanol extract of the oxidation mixture gave another slower-running spot ($R_F = 0{\cdot}37$) with a yellow fluorescence. This material was absent from our ethyl acetate extracts, but on repetition of our experiments using butanol as extractant we also observed this second product in addition to III. This material proved very intractable to chemical treatment and we have not as yet been able to obtain it in pure form. However, we have been able to show that it is not identical with adrenolutine (3,5,6-trihydroxy-l-methylindole) and that it is not a reaction product of adrenolutine and ethylenediamine.

Attention was next turned to noradrenaline. The conditions reported by Burn and Field as optimal (autoxidation at 50°–70° and pH 11) were adopted, and an ethyl acetate extract was chromatographed on alumina as before, yielding a yellow crystalline substance exhibiting an intense green fluorescence in water and ethanol and a blue fluorescence in ethyl acetate. Elementary analysis indicated the empirical formula $C_5H_5N_2$ and this proved at first difficult to interpret, since a compound of such composition cannot be simply derived from the reactants. Weil-Malherbe and Bone observed that under their estimation conditions catechol gave a strong fluorescence, and on repetition of this work on a preparative scale we found that *the same product* (U.V. and I.R. spectrum and behaviour on heating) *is obtained from both catechol and noradrenaline*. We then found that this material can readily be obtained in quantity by the reaction of 2,5-dihydroxybenzoquinone (VIII) with ethylenediamine in hot aqueous solution in the presence of air. This clearly indicated that the empirical formula should be doubled to $C_{10}H_{10}N_4$, and that a tetrahydrotetra-aza-anthracene structure was probable, though the distribution of the hydrogen atoms in this system was not immediately clear, since at least ten alternative possibilities can be written. This matter was settled as follows: 6,7-diaminoquinoxaline (XI) was synthesized by treating 1,2,4,5-tetra-aminobenzene with glyoxal bisulphite. The U.V. spectra of this yellow fluorescent compound and of the tetrahydrotetra-aza-anthracene are given in Fig. 2, and the U.V. spectra of their colourless diacetyl derivatives in Fig. 3. The very close correspondence displayed makes it quite clear that our product is 1,2,3,4-tetrahydro-1,4,5,8-tetra-aza-anthracene (VII). The formation of this compound from catechol via *o*-benzoquinone and an intermediate such as VI does not present any particular chemical difficulties, following a not unusual pattern of quinone–amine condensation, and the same is true of its formation from 2,5-dihydroxybenzoquinone.

However, the formation of VII from noradrenaline is highly unexpected and requires comment. We interpret the reaction as follows: the first stage is the formation

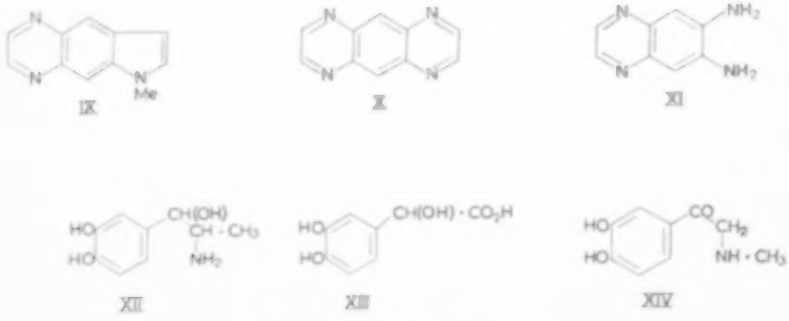


IV V VI

VII VIII

of the *o*-quinone (IV). In the case of adrenaline, cyclization by intramolecular amine-quinone condensation occurs extremely rapidly leading to adrenochrome, but in the noradrenaline case this intramolecular process is slow, possibly due to the lower basicity of the primary amine function. Thus in the noradrenaline case a competing intermolecular process involving reaction with the ethylenediamine (present in large excess) occurs, leading to V. This intermediate then undergoes a further cyclization in which the side-chain is split off by a retro–aldol reaction giving VI, which then reacts further as in the catechol case above.

The above suggested mechanism is easily susceptible of test, since (a) other N-substituted noradrenalines should give products of the type of III and should not give VII; (b) any 4-substituted catechol with a side-chain hydroxyl *alpha* to the benzene ring (other than adrenaline types) should give VII irrespective of the nature of the side-chain; and (c) a 4-substituted catechol without a side-chain hydroxyl in the *alpha* position should not give VII, since elimination of the side-chain by a retro–aldol process would not then be possible. Each of these points has been verified experimentally as follows: (a) N-isopropylnoradrenaline (Isoprenaline) gave a crystalline product whose U.V. spectrum was almost superposable on that of III, and was thus clearly its isopropyl analogue; (b) 2-methylnoradrenaline (XII, Corbasil) and 3,4-dihydroxymandelic acid (XIII) both gave VII in yields comparable to those obtained from noradrenaline; (c) 4-methylcatechol and 3,4-dihydroxyphenylethylamine both gave a mixture of fluorescent products, none of which was identical (paper chromatography) with VII.



IX X XI

XII XIII XIV

Run on paper (butanol–water), the tetrahydrotetra-aza-anthracene had $R_F = 0{\cdot}65$, corresponding very closely to the fast-running product ($R_F = 0{\cdot}64$) reported by

VOL. 7 1959

Burn and Field. These authors also reported a slower-running ($R_F = 0{\cdot}24$) weak spot derived from butanol extracts of noradrenaline–ethylenediamine reactions mixtures, but this we were unable to find. Although stable in the solid state, the tetrahydrotetra-aza-anthracene is photo-sensitive in solution, and on illumination the fluorescence disappears and the initial bright yellow colour becomes pale brown. This effect—presumably a result of photo-oxidation—is extremely marked in very dilute aqueous solution, the fluorescence disappearing in a few minutes on exposure to bright sunlight. This is undoubtedly the explanation of the findings of Goldfien and Karler[5] concerning the sensitivity to light of the noradrenaline estimation. These authors also noted that the adrenaline estimation was not light-sensitive and in agreement with this we find that solutions of the pyrrolo-quinoxaline (III) are quite stable to illumination and the fluorescence does not decay. A further consequence is that paper-chromatography of VII should be conducted in the dark.

We also investigated the behaviour of adrenalone (XIV) in the ethylenediamine reaction. In this case reaction proceeded very slowly and 5 hr heating at 90° was required to produce any substantial amount of fluorescent material. We isolated the product and found again that it was the tetrahydrotetra-aza-anthracene (VII). This was of interest, since the formation mechanism discussed above is not applicable in this case, and we suggest that the reaction here involves slow oxidative degradation of the side-chain ending with protocatechuic acid, which then gives *o*-benzoquinone with loss of carbon dioxide. We indeed confirmed that protocatechuic acid does readily and rapidly give VII with ethylenediamine and this finding is not surprising in view of the fact that the acid is known to give *o*-benzoquinone with decarboxylation on chemical oxidation. It may be noted in passing that on mechanistic grounds adrenalone might be expected to cyclize and give adrenolutine on oxidation, but numerous attempts to achieve this[6] proved unsuccessful, though the reasons for failure are not obvious.

Under normal conditions of oxidation, no trace of VII could be found in experiments with adrenaline; however, in one autoxidation experiment in which the mixture had been heated for 3 hr and then left standing for several days, a small amount of VII was isolated in addition to a larger amount of the normal product (III). We suggest that under these conditions, a small amount of adrenaline is autoxidized to adrenalone rather than to adrenochrome, and it is this adrenalone which gives rise to VII as above. It may also be noted that the noradrenaline analogue of III was never encountered in any of our experiments, and does not appear to be formed at all.

The chemistry of the tetrahydrotetra-aza-anthracene (VII) was further examined. On heating, the material does not melt, but decomposes at about 300° giving a small amount of almost colourless crystalline sublimate. This material gave analytical figures corresponding to a molecular formula of $C_{10}H_6N_4$ and its U.V. spectrum resembled that of phenazine. The same product was obtained in better yield when the tetrahydro compound was dehydrogenated with palladium–charcoal in boiling nitrobenzene. Evidently this product was fully aromatic 1,4,5,8-tetra-aza-anthracene (X), and formed almost colourless long needles giving pale yellow non-fluorescent solutions in water and ethanol and orange-yellow solutions in mineral acids. The

[5] A. Goldfien and R. Karler, *Science* **127**, 1292 (1958).
[6] J. D. Bu'Lock and J. Harley-Mason, unpublished.

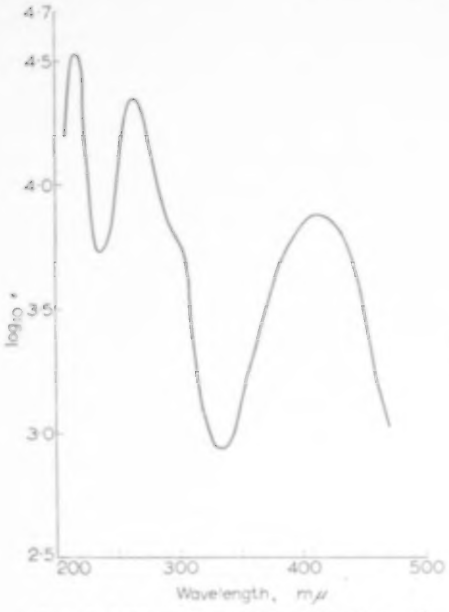


FIG. 1. Ultra-violet absorption spectrum of 2,3-dihydro-3-hydroxy-1-methylpyrrolo-4,5-g-quinoxaline (III).

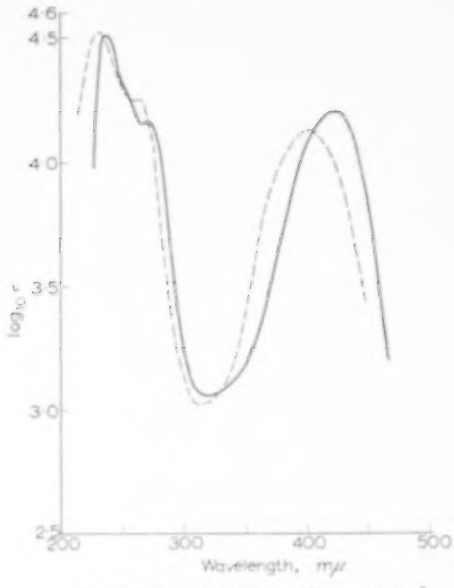


FIG. 2. Ultra-violet absorption spectra of:
——— 1,2,3,4-tetrahydro-1,4,5,8-tetra-aza-anthracene (VII).
– – – – 6,7-diaminoquinoxaline (XI).

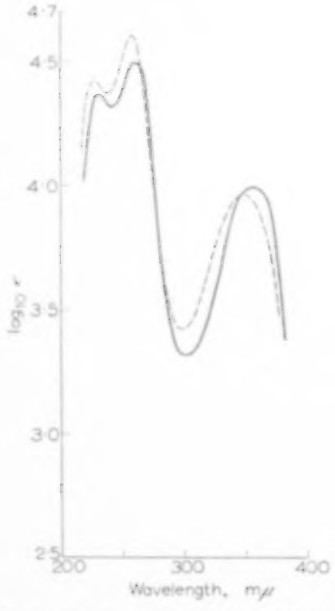


FIG. 3. Ultra-violet absorption spectra of:
——— 1,4-diacetyl-1,2,3,4-tetrahydro-1,4,5,8-tetra-aza-anthracene.
– – – – N N′-diacetyl-6,7-diaminoquinoxaline.

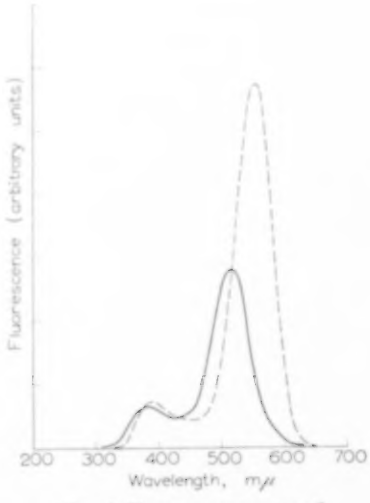


FIG. 4. Fluorescence spectra of:
——— 1,2,3,4-tetrahydro-1,4,5,8-tetra-aza-anthracene (VII). (Activation 295 mμ.)
– – – – 2,3-dihydro-3-hydroxy-1-methylpyrrolo-4,5-g-quinoxaline (III). (Activation 285 mμ.)

ethanolic solution was photo-sensitive, like that of the tetrahydro compound, but in this case, on illumination, a yellow colour and an intense green fluorescence developed. The tetrahydro compound dissolves in mineral acids giving deep red non-fluorescent solutions, and a dark red dihydrochloride was characterized. Fluorescence spectra of III and VII are given in Fig. 4.

A preliminary account of some of this work has been given earlier.[7]

EXPERIMENTAL

Ultra-violet spectra were determined in 95 per cent ethanol using a Cary recording spectrophotometer. Melting points are uncorrected.

VOL. 7 1959

Oxidative reaction of adrenaline with ethylenediamine

(a) L-Adrenaline (1 g) was dissolved in methanol (150 ml) containing formic acid (1 ml). Silver oxide (3 g) was added, and the mixture shaken for 7 min. The red solution of adrenochrome thus obtained was then filtered, and ethylenediamine (7 ml) added. After standing for 10 min, the solution was diluted with water (500 ml) and extracted with ethyl acetate (15 × 100 ml). The combined extracts were dried (Na_2SO_4), concentrated to small bulk, and chromatographed on an alumina column (15 cm × 1 cm^2). Elution of the bright yellow band with ethyl acetate–methanol (9 : 1), and evaporation of the eluate gave a yellow solid. Recrystallization from a small volume of ethyl acetate gave (−)-2,3-*dihydro*-3-*hydroxy*-1-*methylpyrrolo*-4,5 g-*quinoxaline* (III) (80 mg) as fine yellow needles, m.p. 171–172°, $[\alpha]_D^{20°} \approx -80°$ (ethanol, *c*, 0·7) (Found: C, 65·2; H, 5·6; N, 20·7. $C_{11}H_{11}ON_3$ requires: C, 65·6; H, 5·6; N, 20·9%). The product is readily soluble in water and the common organic solvents giving bright yellow solutions with an intense green fluorescence. The R_F in n-butanol–water was 0·69.

(b) L-Adrenaline (200 mg) was dissolved in dilute H_2SO_4 (1 ml) and an aqueous solution of ethylenediamine (5%; 100 ml) added. The solution was heated at 60° for 1·5 hr while a stream of air was drawn through it. After cooling, the mixture was extracted with ethyl acetate and worked up as before to give 15 mg of the same product.

(c) L-Adrenaline (200 mg) was treated as above, but in this case the reaction mixture was extracted with n-butanol (5 × 30 ml) instead of ethyl acetate. The butanol was removed *in vacuo* and the gummy residue was boiled with ethyl acetate (5 ml) and filtered. The filtrate was chromatographed on alumina as before, but in this case two yellow zones appeared. The faster-running material was eluted with ethyl acetate–ethanol (95 : 5) and proved to be the above pyrroloquinoxaline. The slower-running material was eluted with ethanol, and removal of the solvent gave a yellow amorphous product giving solutions displaying a strong yellow fluorescence. Further attempts at purification were unsuccessful. Run on paper (butanol–water) the material gave a rather diffuse spot of R_F approx. 0·36. A red colour was given with Ehrlich's reagent and a transient red colour with HCl. Light-absorption max, 262, 360 and 420 mμ.

1-*Methylpyrrolo*-4,5-g-*quinoxaline* (IX)

The foregoing hydroxy compound (25 mg) was dissolved in 3N HCl (2 ml), and the deep red solution was boiled for 3 min, cooled, and made alkaline with NaOH. The precipitated solid was collected, recrystallized from water, and then sublimed at 90°/10^{-4}mm, giving 1-*methylpyrrolo*-4,5-g-*quinoxaline* (20 mg) as yellow needles, m.p. 141–142°. (Found: C, 72·4; H, 4·9. $C_{11}H_9N_3$ requires: C, 72·1; H, 4·9%). The same product was obtained on boiling the hydroxy compound with acetic anhydride for 15 min. Light-absorption max, 226, 266, 352 and 410 mμ (ε, 24,000, 30,000, 8000 and 2000 respectively).

Oxidative reaction of noradrenaline with ethylenediamine

L-Noradrenaline bitartrate (250 mg) was dissolved in a 5% aqueous solution of ethylenediamine (125 ml) adjusted to pH 11 with H_2SO_4. The mixture was heated to 60° for 2 hr while a stream of air was drawn through it. The cooled solution was extracted with ethyl acetate (6 × 50 ml), the extracts dried (Na_2SO_4), and concentrated to small bulk. The concentrate was chromatographed on an alumina column (10 cm × 1 cm), the yellow band eluted with ethyl acetate, and the eluate

[7] J. Harley-Mason and A. H. Laird, *Biochem. J.* **69**, 59P (1958).

evaporated to give a yellow solid. This was recrystallized from ethanol giving 1,2,3,4-*tetrahydro*-1,4,5,8-*tetra-aza-anthracene* (VII, 40 mg) as small yellow plates (Found: C, 64·2; H, 5·6; N, 29·6. $C_{10}H_{10}N_4$ requires: C, 64·5; H, 5·4; N, 30·1%). The compound decomposes without melting at about 300° giving a sublimate of almost colourless needles (see below). The compound is soluble in water, ethanol and methanol giving yellow solutions with a powerful green fluorescence. In less polar solvents such as ethyl acetate, the fluorescence is blue. Treatment with ethanolic HCl gave a *dihydrochloride*, deep red prisms from aqueous ethanol (Found: C, 45·9; H, 4·3; N, 20·8. $C_{10}H_{10}N_4$. 2HCl requires: C, 46·4; H, 4·6; N, 21·6%). Light-absorption max, 262 and 478 mμ (ε, 39,000 and 25,000 respectively).

Boiling with acetic anhydride gave a *diacetyl derivative* which formed white needles from ethanol, m.p. 244–245° (Found: C, 62·3; H, 5·3; N, 20·7. $C_{14}H_{14}O_2N_4$ requires: C, 62·2; H, 5·2; N, 20·8%).

Other reactions leading to 1,2,3,4-*tetrahydrotetra-aza-anthracene*

(a) When the above experiment was repeated using 2-methyl noradrenaline and 3,4-dihydroxymandelic acid the same product was obtained in comparable yield in each case.

(b) Using adrenalone the above experiment was repeated except that the temperature was raised to 90° and the heating continued for 6 hr. The tetrahydrotetra-aza-anthracene was obtained as before.

(c) 2,5-Dihydroxy-*p*-benzoquinone (4·7 g) was dissolved in boiling water (300 ml), and ethylenediamine (10 ml) was added. The mixture was heated at 95° for 1 hr while a stream of air was drawn through it. After cooling, the brownish-yellow solid was filtered off and twice recrystallized from aqueous ethanol, giving the tetrahydrotetra-aza-anthracene (3 g; 50%). This is the most convenient method of preparation.

(d) A solution of catechol (12·5 g) and ethylenediamine (51 g) in water (1·0 l.) was heated at 50° for 2·5 hr while a stream of air was drawn through it. After cooling, the brown solution was extracted with ethyl acetate (5 × 100 ml), the combined extracts dried (Na_2SO_4), and the solvent removed, leaving a yellow solid. This was dissolved in dilute HCl (75 ml) and extracted five times with ether to remove unreacted catechol. The red aqueous phase was basified and then extracted with ethyl acetate (5 × 50 ml). Evaporation of this extract gave the tetrahydrotetra-aza-anthracene (50 mg).

1,4,5,8-*Tetra-aza-anthracene* (X)

(a) The tetrahydro compound (1·5 g) was refluxed in nitrobenzene (250 ml) with 10% Pd-charcoal (1 g) for 4 hr. After cooling and filtering, water was added and the mixture steam-distilled for 6 hr to remove nitrobenzene. The aqueous solution was concentrated, yielding a crude product which on recrystallization from water (charcoal) gave 1,4,5,8-*tetra-aza-anthracene* (0·5 g) as long, very pale yellow needles, m.p. 215–216°. For analysis, a sample was sublimed at 160°/10^{-3}mm (Found: C, 65·6; H, 3·0; N, 30·7. $C_{10}H_6N_4$ requires: C, 65·8; H, 3·3; N, 30·8%). Light-absorption max, 243 and 353 mμ (ε, 70,000 and 10,000 respectively). The compound is soluble in water and ethanol giving almost colourless non-fluorescent solutions; however, on exposure to light the solutions slowly turn yellow and acquire a green fluorescence.

(b) The tetrahydro compound (75 mg) was placed in a long glass tube heated in a sublimation block. When the temp was raised to 300°, the tetra-aza-anthracene (10 mg) sublimed out of the decomposing material as long needles, m.p. 215–216°.

6,7-*Diaminoquinoxaline* (XI)

To a solution of 1,2,4,5-tetra-aminobenzene hydrochloride[a] (0·5 g) and glyoxal bisulphite (0·5 g) in water (7 ml), solid $NaHCO_3$ was added until no more CO_2 was evolved. After warming briefly and then cooling, a yellowish-red crystalline solid separated, and was at once collected and recrystallized from water (charcoal), giving 6,7-*diaminoquinoxaline* (30 mg) as fine yellow needles, m.p. >360° (Found: C, 59·3; H, 5·4; N, 35·0. $C_8H_8N_4$ requires: C, 60·0; H, 5·0; N, 35·0%). Boiling with acetic anhydride gave the diacetyl derivative which formed colourless needles, m.p. 279–280° from ethanol.

Acknowledgements—The authors thank Professor R. T. Williams for permission to use the spectrophotofluorimeter at St. Mary's Hospital, London. One of us (A. H. L.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

[a] R. Nietzki and E. Hagenbach, *Ber. Dtsch. Chem. Ges.* **20,** 328 (1887).

Tetrahedron, 1959, Vol. 7, pp. 77 to 81. Pergamon Press Ltd. Printed in Northern Ireland

RING-ISOMERIC CHANGE IN ISOFLAVONES

SYNTHESIS OF 5,7-DIMETHOXY-6-HYDROXYISOFLAVONE, MUNINGIN AND 5,7-DIHYDROXY-6-METHOXYISOFLAVONE

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VOL. 7 1959

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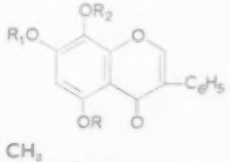
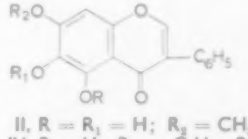
Abstract—The above mentioned compounds have been prepared by methods involving isomeric change from the more readily available 5,7,8-substituted isoflavones.

RING isomeric change in flavonoids, the Wessely–Moser rearrangement[1] has been investigated in detail in recent years.[2] The rearrangement takes place with chromones and flavones in strongly acid medium but does not proceed satisfactorily in the case of isoflavones. Isoflavones isomerise under alkaline conditions[3] and Mahesh and Seshadri[4] showed that 5-hydroxy-7,8-dimethoxyisoflavone can be converted into the isomeric 5-hydroxy-6,7-dimethoxyisoflavone by treatment with alcoholic potash. This is useful because the former is more easily prepared. This method of isomeric change has now been applied for the synthesis of a few isoflavones substituted in the 5,6,7-positions and belonging to the types occurring in nature.

5,8-Dihydroxy-7-methoxyisoflavone[5] (I) was obtained by the controlled demethylation of 5,7,8-trimethoxyisoflavone with hydriodic acid. It isomerized in alcoholic potash giving poor yields of 5,6-dihydroxy-7-methoxy-isoflavone (II)[6,7]; better yields were obtained in a hydrogen atmosphere. 8-Benzyloxy-5-hydroxy-7-methoxyisoflavone (III) obtained by the partial benzylation of the dihydroxy isoflavone (I) gave satisfactory yields of 6-benzyloxy-5-hydroxy-7-methoxyisoflavone (IV). It was then methylated to give 6-benzyloxy-5,7-dimethoxyisoflavone (V) which on debenzylation with hydrogen and Raney-nickel gave 6-hydroxy-5,7-dimethoxy isoflavone[8] (VI); hydrochloric acid was unsuitable since it produced demethylation in the 5-position.



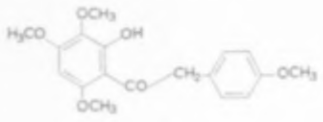
I, R = R_2 = H; R_1 = CH_3
III, R = H; R_1 = CH_3; R_2 = C_7H_7



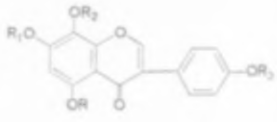
II, R = R_1 = H; R_2 = CH_3
IV, R = H; R_1 = C_7H_7; R_2 = CH_3
V, R = R_2 = CH_3; R_1 = C_7H_7
VI, R = R_2 = CH_3; R_1 = H

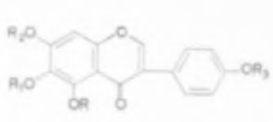
[1] F. Wessely and G. H. Moser, *Monatsh.* **56**, 97 (1930).
[2] S. K. Mukerjee and T. R. Seshadri, *Chem. & Ind.* 271 (1955).
[3] V. B. Mahesh, N. Narasimhachari and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **39 A**, 165 (1954).
[4] V. B. Mahesh and T. R. Seshadri, *J. Sci. Industr. Res. India* **14 B**, 671 (1955).
[5] Ishwar Dass, N. Narasimhachari and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **37 A**, 599 (1953).
[6] S. S. Karmarkar, K. M. Shah and K. Venkataraman, *Proc. Ind. Acad. Sci.* **41 A**, 192 (1955).
[7] K. Aghoramurthy, T. R. Seshadri and G. B. Venkatasubramanian, *J. Sci. Industr. Res.* **15 B**, 11 (1956).
[8] M. L. Dhar and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **43 A**, 79 (1956).

For the synthesis of muningin, the intermediate 2-hydroxy-3,4,6,4′-tetramethoxyphenylbenzyl ketone (VII) was prepared by the Friedel and Crafts reaction using 1,2,3,5-tetramethoxybenzene and *p*-methoxyphenylacetyl chloride. Ring closure using the ethyl formate and sodium method[9] yielded 5,7,8,4′-tetramethoxyisoflavone (VIII) which on partial demethylation with hydriodic acid[5] gave 5,8,4′-trihydroxy-7-methoxyisoflavone (IX). Benzylation gave 8,4′-dibenzyloxy-5-hydroxy-7-methoxyisoflavone (X) which isomerized into 6,4′-dibenzyloxy-5-hydroxy-7-methoxyisoflavone (XI). Subsequent methylation gave muningin dibenzyl ether (XII) and final debenzylation yielded muningin (XIII), identical with the natural sample[10] and also that synthesized previously.[5]



VII

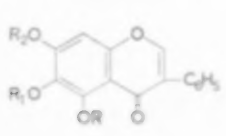


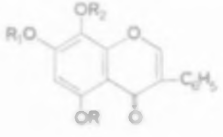


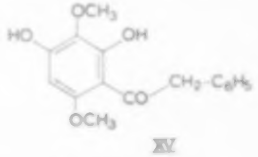
VIII, R = R_1 = R_2 = R_3 = CH_3
IX, R = R_2 = R_3 = H; R_1 = CH_3
X, R = H; R_1 = CH_3; R_2 = R_3 = C_7H_7

XI, R = H; R_2 = CH_3; R_1 = R_3 = C_7H_7
XII, R = R_2 = CH_3; R_1 = R_3 = C_7H_7
XIII, R = R_2 = CH_3; R_1 = R_3 = H

In view of the difficulties originally experienced in the synthesis of tectorigenin, it was considered useful to extend the method of ring isomeric change for its synthesis. In exploratory experiments the simpler analogue, 5,7-dihydroxy-6-methoxyisoflavone (XIV) has been synthesized successfully. 2,4-Dihydroxy-3,6-dimethoxyphenylbenzyl ketone (XV) was obtained by the Hoesch reaction of 2,6-dibenzyloxy-1,4-dimethoxybenzene and phenylacetonitrile and converted into 7-hydroxy-5,8-dimethoxyisoflavone (XVI). Partial demethylation with anhydrous aluminium chloride or concentrated hydrochloric acid gave 5,7-dihydroxy-8-methoxyisoflavone (XVII) which on treatment with alcoholic potash isomerized to 5,7-dihydroxy-6-methoxyisoflavone (XIV). It was also prepared from 5,6,7-trihydroxyisoflavone which was benzylated in the 7-position (XVIII) followed by partial methylation (XIX) and dedenzylation with acetic acid and hydrochloric acid. Isomerization has not so far been successful in the case of the corresponding 4′-hydroxy substituted isoflavone and tectorigenin was not obtained.







XV

XIV, R = R_2 = H; R_1 = CH_3
XVIII, R = R_1 = H; R_2 = C_7H_7
XIX, R = H; R_1 = CH_3; R_2 = C_7H_7

XVI, R = R_2 = CH_3; R_1 = H
XVII, R = R_1 = H; R_2 = CH_3

XV

EXPERIMENTAL

5,6-Dihydroxy-7-methoxyisoflavone (II)

A solution of 5,8-dihydroxy-7-methoxyisoflavone[5] (1 g) in alcoholic potash (100 cc, 2%) was refluxed for ½ hr under hydrogen, cooled to 0°, acidified with HCl and the precipitated isoflavone

[9] P. C. Joshi and K. Venkataraman, *J. Chem. Soc.* 513 (1934).
[10] F. E. King, T. J. King and A. J. Warwick, *J. Chem. Soc.* 96 (1952).

collected and crystallized from alcohol; colourless silky needles (0·15 g) m.p. and mixed m.p. with an authentic sample[8] 222–224°.

8-Benzyloxy-5-hydroxy-7-methoxyisoflavone (III)

5,8-Dihydroxy-7-methoxyisoflavone (3 g) in dry acetone (300 cc) was treated with benzyl chloride (1·2 cc) anhydrous potassium carbonate (10 g) and anhydrous sodium iodide (2·5 g) and the mixture refluxed for 9 hr. The *benzyloxy isoflavone* crystallized from alcohol as colourless rectangular prisms (1·9 g), m.p. 106–108°. It gave a green colour with ferric chloride and was sparingly soluble in 5% aqueous sodium hydroxide (Found: C, 74·2; H, 5·1; $C_{23}H_{18}O_5$ requires: C, 73·7; H, 4·8%).

6-Benzyloxy-5-hydroxy-7-methoxyisoflavone (IV)

III (1 g) was isomerized with alcoholic potash (100 cc; 2%) as before but without hydrogen. The *isoflavone* crystallized from alcohol as colourless rhombohedral plates (0·5 g) m.p. 174–176°. The mixed m.p. with an authentic sample of 6-benzyloxy-5-hydroxy-7-methoxy isoflavone prepared by the partial benzylation of 5,6-dihydroxy-7-methoxy isoflavone showed no depression. It gave a green colour with ferric chloride and was sparingly soluble in 5% aqueous sodium hydroxide (Found: C, 73·2; H, 4·6; $C_{23}H_{18}O_5$ requires: C, 73·7; H, 4·8%).

6-Benzyloxy-5,7-dimethoxyisoflavone (V)

Prepared by the methylation of 6-benzyloxy-5-hydroxy-7-methoxyisoflavone using methyl sulphate, acetone and potassium carbonate, the *methyl ether* was obtained as small rectangular prisms from alcohol m.p. 154–155°. It gave no colour with ferric chloride and was insoluble in aqueous sodium hydroxide (Found: C, 73·7; H, 5·4; $C_{24}H_{20}O_5$ requires: C, 74·2; H, 5·1%).

6-Hydroxy-5,7-dimethoxyisoflavone (VI)

The methyl ether (V) (0·5 g) in alcohol (300 cc) was treated with Raney nickel (1·5 g) and a slow stream of hydrogen was passed for ½ hr with occasional shaking. The solution was filtered and the filtrate evaporated under reduced pressure. The residue crystallized from dilute alcohol yielding the *isoflavone* as colourless thick rectangular tablets and plates (0·15 g) m.p. 184–186°. It was easily soluble in dilute aqueous sodium hydroxide (Found: C, 68·1; H, 5·0; $C_{17}H_{14}O_5$ requires: C, 68·4; H, 4·7%). The *acetate* crystallized from alcohol as colourless thick rectangular tablets, m.p. 205–207°.[8]

2-Hydroxy-3,4,6,4′-tetramethoxyphenylbenzyl ketone (VII)

To a solution of anhydrous aluminium chloride (20 g) in ether (200 cc) at 0°, 1,2,3,5,-tetramethoxy benzene (10 g) in ether was added, followed by *p*-methoxyphenylacetyl chloride (8 cc). The mixture was cooled in ice for 2 hr and subsequently left at room temp for 12 hr. Ether was removed and the residue decomposed with ice and HCl and heated (water-bath) for 1 hr. The ketone separated as an oil on cooling and was extracted with ether, and the ether solution washed first with aqueous sodium bicarbonate, and then with water and finally dried over anhydrous sodium sulphate.

Evaporation of ether gave the *ketone* as a dark viscous mass which crystallized from alcohol as pale yellow prisms (9·0 g) m.p. 119–120°. It gave a reddish brown colour with alcoholic ferric chloride (Found: C, 65·3; H, 6·1; $C_{18}H_{20}O_6$ requires: C, 65·0; H, 6·0%).

5,7,8,4′-Tetramethoxyisoflavone (VIII)

Prepared from VII (2 g) by cyclization with ethyl formate (20 cc) in presence of powdered sodium (1 g), the *isoflavone* was obtained from ethyl acetate as long rectangular tablets (1·0 g) m.p. 147–149° (Found: C, 66·2; H, 5·3; $C_{19}H_{18}O_6$ requires: C, 66·6; H, 5·2%).

5,8,4′-Trihydroxy-7-methoxyisoflavone (IX)

Tetramethoxy isoflavone (VIII, 1 g) in acetic anhydride (10 cc) was heated with hydriodic acid (10 cc, *d* 1·7) at 120° for ½ hr. After cooling and decolourizing with sulphurous acid, the solid was collected and crystallized from alcohol yielding pale yellow rectangular plates of the *isoflavone* (0·6 g) m.p. 268–270° (*d*) with sintering at 240°. It gave a green colour with alcoholic ferric chloride and was easily soluble in aqueous sodium carbonate (Found: C, 63·9; H, 3·9; $C_{16}H_{12}O_6$ requires: C, 64·0; H, 4·0%).

VOL. 7 1959

8,4′-*Dibenzyloxy*-5-*hydroxy*-7-*methoxyisoflavone* (X)

A solution of IX was partially benzylated with benzyl chloride (2 moles) as described before, and the *dibenzyl ether* crystallized from ethyl acetate–light petroleum as colourless rhombohedral tablets (0·5 g) m.p. 102–104°. It gave an olive green colour with alcoholic ferric chloride and was sparingly soluble in aqueous sodium hydroxide (Found: C, 74·6; H, 4·9; $C_{30}H_{24}O_6$ requires: C, 75·0; H, 5·0%).

6,4′-*Dibenzyloxy*-5-*hydroxy*-7-*methoxyisoflavone* (XI)

X (0·5 g) was isomerized with alcoholic potash (50 cc, 2%). The *isoflavone* (XI) crystallized from alcohol as colourless rectangular prisms (0·25 g) m.p. 182–184°. It gave a green colour with alcoholic ferric chloride and was sparingly soluble in aqueous sodium hydroxide (Found: C, 74·8; H, 5·2; $C_{30}H_{24}O_6$ requires: C, 75·0; H, 5·0%).

6,4′-*Dibenzyloxy*-5,7-*dimethoxyisoflavone* (XII)

Prepared by the methylation of XI (0·5 g) with excess of dimethyl sulphate, acetone and potassium carbonate, the *benzyl methyl ether* crystallized from alcohol as colourless rectangular rods (0·3 g) m.p. 246° (*d*) (Found: C, 74·9; H, 5·7; $C_{32}H_{28}O_6$ requires: C, 75·3; H, 5·2%).

6,4′-*Dihydroxy*-5,7-*dimethoxyisoflavone* (*muningin* XIII)

The above benzyl methyl ether (0·5 g) in alcohol (700 cc) was debenzylated with Raney nickel (1·5 g) and hydrogen. The *hydroxy isoflavone* crystallized from dioxan as colourless rectangular tablets (0·1 g) m.p. 285°. It gave no colour with alcoholic ferric chloride and dissolved in aqueous alkali giving a yellow solution which turned red on heating. It also developed a red colour with conc H_2SO_4 and a trace of conc HNO_3. It was identical with a natural sample of muningin[10] and mixed m.p. was undepressed (Found: C, 64·5; H, 4·8; $C_{17}H_{14}O_6$ requires: C, 65·0; H, 4·5%). The *acetate* crystallized from alcohol as colourless needles m.p. 230–232° agreeing with an authentic sample.

7-*Benzyloxy*-5,6-*dihydroxyisoflavone* (XVIII)

5,6,7-Trihydroxy isoflavone (2 g) in dry acetone (200 cc) was refluxed with benzyl chloride (0·84 cc, 1 mole), sodium iodide (1 g) and sodium bicarbonate (6 g) for 24 hr. The *benzyl ether* crystallized from alcohol as colourless long needles (0·7 g) m.p. 234–236°. It gave a green colour with alcoholic ferric chloride (Found: C, 73·4; H, 4·9; $C_{22}H_{16}O_5$ requires: C, 73·3; H, 4·4%).

7-*Benzyloxy*-5-*hydroxy*-6-*methoxyisoflavone* (XIX)

XVIII (1 g), dry acetone (200 cc), dimethylsulphate (0·22 cc, 1 mole) and anhydrous potassium carbonate (5 g) were heated for 6 hr. The *methyl ether* crystallized from alcohol as rectangular prisms (0·6 g) m.p. 184–186° and gave a reddish violet colour with alcoholic ferric chloride (Found: C, 73·4; H, 4·9; $C_{23}H_{18}O_5$ requires: C, 73·7; H, 4·8%).

5,7-*Dihydroxy*-6-*methoxyisoflavone* (XIV)

XIX (0·4 g) was debenzylated by heating with glacial acetic acid (30 cc) and conc HCl (4 cc) for 1½ hr. The *hydroxy isoflavone* crystallized from ethyl acetate–light petroleum as long prismatic needles (0·2 g) m.p. 154–156°. It was soluble in aqueous sodium carbonate (5%) and gave a reddish violet colour with ferric chloride which changed to deep green with excess of the reagent (Found: C, 67·3; H, 4·3; $C_{16}H_{12}O_5$ requires: C, 67·6; H, 4·2%). The *acetate* was obtained from alcohol as colourless needles, m.p. 162–164° (Found: C, 64·6; H, 4·7; $C_{20}H_{16}O_7$ requires: C, 65·2; H, 4·3%).

2,4-*Dihydroxy*-3,6-*dimethoxyphenylbenzyl ketone* (XV)

Dry hydrogen chloride was passed through a mixture of 2,6-dibenzyloxy-1,4-dimethoxy benzene (10 g), zinc chloride (4 g) and benzyl cyanide (3·4 cc) in dry ether (150 cc), cooled in a freezing mixture. After 2 hr the freezing mixture was replaced by ice and the passage of hydrogen chloride continued for another 6 hr. The mixture was left in the ice chest for 2 days; the oily ketimine hydrochloride was washed with ether, dissolved in hot water, the solution allowed to remain at room temp for 2 hr and finally heated at 100° for 1 hr. On cooling, the ketone separated out as a dark oil. It was extracted

with ether and the ether solution washed with aqueous bicarbonate. Subsequent extraction with aqueous sodium carbonate (10%) and acidification of the extract yielded the ketone as an almost colourless solid which crystallized from benzene–light petroleum mixture as long prismatic needles (5 g) m.p. 101–102°. It gave a reddish violet colour with alcoholic ferric chloride (Found: C, 66·1; H, 5·4; $C_{16}H_{14}O_5$ requires: C, 66·6; H, 5·5%.).

7-*Hydroxy*-5,8-*dimethoxyisoflavone* (XVI)

XV (2 g) was cyclized using methyl formate (40 cc) and powdered sodium (1 g); the *isoflavone* crystallized from ethanol as colourless prisms (0·2 g) m.p. 254–256° with sintering at 240°. It was soluble in aqueous sodium hydroxide and sodium carbonate but gave no colour with ferric chloride (Found: C, 68·7; H, 4·7; $C_{17}H_{14}O_5$ requires: C, 68·4; H, 4·6%).

5,7-*Dihydroxy*-8-*methoxyisoflavone* (XVII)

(a) 7-Hydroxy-5,8-dimethoxyisoflavone (0·5 g) in dry nitrobenzene (50 cc) was treated with anhydrous aluminium chloride (0·45 g, 2 mole), and heated (water-bath) for 1 hr and nitrobenzene removed by steam distillation. The residue was treated with dilute HCl and heated (water-bath) for ½ hr. After cooling the isoflavone separated as a solid which crystallized from ethyl acetate–light petroleum mixture as colourless prisms (0·2 g) m.p. 174–176°. It gave a reddish violet colour with alcoholic ferric chloride which changed to green with excess of the reagent (Found: C, 67·5; H, 4·4; $C_{16}H_{12}O_5$ requires: C, 67·6; H, 4·2%).

(b) The same product (0·1 g) was obtained by refluxing XVI (0·2 g) in dioxane (5 cc) with conc HCl (2 cc) for 4 hr, removing dioxane under reduced pressure, adding water and crystallizing the solid.

5,7-*Dihydroxy*-6-*methoxyisoflavone* (XIV)

XVII (0·3 g) was isomerized with alcoholic potash (30 cc, 2%), and the isomeric *isoflavone* crystallized from ethyl acetate–light petroleum mixture as colourless long prismatic needles (0·15 g) m.p. and mixed m.p. 154–156°.

We convey thanks to Prof. F. E. King for a sample of natural muningin.

VOL. 7 1959

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STEREOCHEMICAL IMPLICATIONS IN SESQUITERPENE BIOGENESIS

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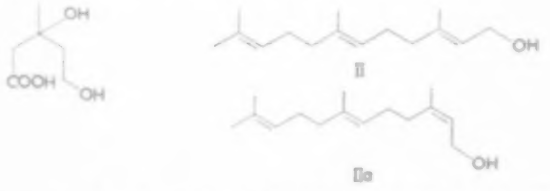
Abstract—The biogenesis of the sesquiterpenes is envisioned as a displacement of the allylic hydroxyl of farnesol by either of the isolated double bonds, giving rise to versatile 6-, 10-, or 11-membered ring intermediates. The medium-ring intermediates possess unique conformations which dictate the structure as well as stereochemistry of the sesquiterpenes derived from them by a variety of simple further reactions, notably double-bond cyclizations.

THE domain of terpene biogenesis, which was for too long a haven for undisciplined speculation, has been brilliantly codified and extended in recent years by the Swiss group of Ruzicka, first in an original and authoritative presentation of the entire field in 1953,[1] and then in the elegant conception of triterpene and steroid biogenesis[2] which must rank as a model of the critical approach to this speculative realm which is made possible by the application of modern reaction theory and the stereochemical limits implicit in it. An attempt is made here to apply this approach to sesquiterpene biogenesis, extending the ideas of Ruzicka[1] and Barton[3] on the involvement of large rings in order to incorporate stereochemical features.

It now seems clear that the actual isoprenoid unit utilized in terpene biosynthesis is mevalonic acid (I),[4] three molecules of which (or an appropriately activated simple derivative) can self-condense with decarboxylation directly to farnesol (II),* the simplest acyclic sesquiterpene. It should be noted that this conversion yields farnesol



II IIa

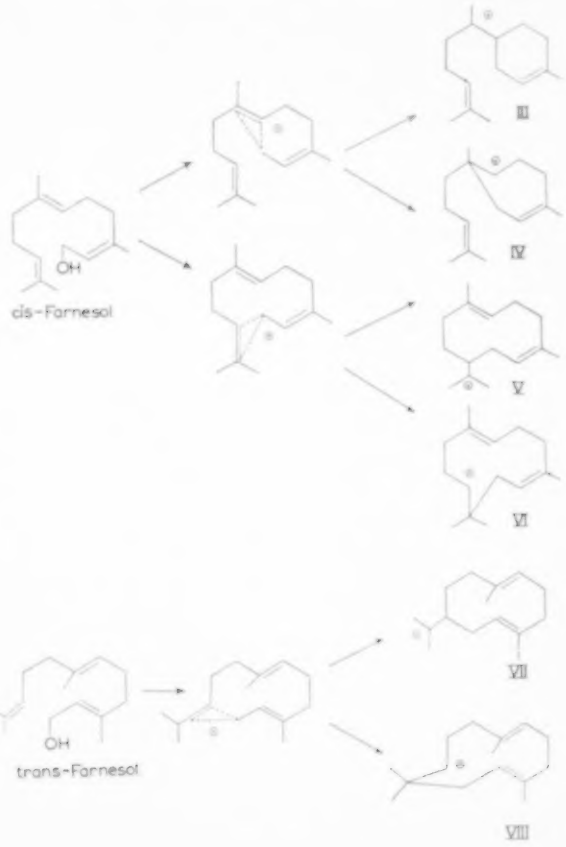
without any change in oxidation state and with its double bonds all anchored at the tertiary carbons initially occupied by the hydroxyl in mevalonic acid. Farnesol is isolated from natural sources as a complex mixture of double bond isomers, but it is assumed here by analogy with squalene that the original farnesol produced from

* Unless otherwise indicated, all structures herein are taken from Sir John Simonsen, *The Terpenes* (2nd Ed.), Vols. III and V, Cambridge University Press (1952, 1957) and reference (3), and original references contained therein.

[1] L. Ruzicka, *Experientia* **9**, 357 (1953).
[2] A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta* **38**, 1890 (1955); L. Ruzicka in *Perspectives in Organic Chemistry* (ed. by A. Todd) pp. 265. Cambridge University Press (1956).
[3] D. H. R. Barton and P. de Mayo, *Quart. Rev.* **11**, 189 (1957).
[4] D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, *J. Amer. Chem. Soc.* **78**, 4499 (1956); B. H. Amdur, H. Rilling and K. Bloch, *Ibid.* **79**, 2646 (1957); A. J. Birch, R. J. English, R. A. Massy-Westropp and H. Smith, *Proc. Chem. Soc.* 233 (1957).

mevalonic acid has the trans central bond. However, it is known that the allylic double bond can be found in both *cis*- and *trans*-orientations, via anionotropic conversion through nerolidol, the corresponding tertiary allylic alcohol. It will be argued below that *cis*-farnesol (IIa) or *trans*-farnesol (II) is a reasonable precursor for cyclization to all the cyclic sesquiterpenes.

The lowest and most common oxidation state of the cyclic sesquiterpenes is the same as that of farnesol, implying that the cyclization proceeds without oxidation and hence is a different process from that occurring in squalene cyclization to the triterpenes. The biogenesis of the sesquiterpenes from farnesol is considered[1] to involve ionization of the allylic hydroxyl and cyclization of one of the other double bonds to the cation thus formed. Thus, we may envision that one of the isolated double bonds can assist in the ionization of the allylic hydroxyl if its π-electrons can be oriented by coiling the chain so that they overlap with the generating π-orbital of the allylic cation.* Such species can then collapse by solvent attack or deprotonation to give the products expected from neutralization of the simple cations (III) through (VIII).



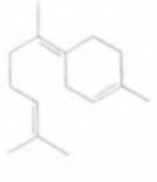
* The detailed mechanism is not germane to our purpose, for even if the cyclization is considered to be a simple displacement of —OH by the π-electrons of the double bond, the stereochemical requirements to be discussed will be the same.

VOL. 7 1959

If we now consider in detail the various possibilities of cyclizing *cis*- and *trans*-farnesol, we can see that utilization of the central double bond is only possible with *cis*-farnesol, and that both electronic and steric factors combine to favor the intermediacy of the cation (III) rather than (IV). The monocyclic 6-ring sesquiterpenes do in fact all have this skeleton and generally possess the same pattern of oxidized sites on the skeleton, as in bisabolene (IIIa), which simply derives from (III) by deprotonation.

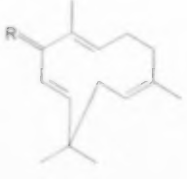
The question of utilization of the terminal double bond is more interesting. Models make it clear that *cis*- and *trans*-farnesol can each fold in such a way as to allow cyclization to products of the four intermediate cations (V), (VI), (VII) and (VIII). Furthermore, each of these ions has a *single, unique conformation dictated by maximum π-overlap and minimum steric interference* in the process of attack by the isolated double bond on the allylic alcohol. The *cis*, 10-ring cation (V) is, however, much more strained than the 11-ring cation (VI) and the models suggest that the latter will form by preference, i.e., steric rather than electronic control of the cyclization. From *trans*-farnesol, the cation (VII) is sterically as well as electronically favored over its rival (VIII). Thus the large body of sesquiterpenes which arise by cyclization involving the terminal bond can be shown to arise either from *cis*-farnesol via (VI) or from *trans*-farnesol via (VII).

Models of the *cis*-cation (VIa) reveal two interesting features: (a) the double bonds are not very close to each other for internal cyclization; and (b) one of the hydrogens on C_1 is turned inside the ring, lying somewhat between C_6 and the cationic C_{10}. Examining the various ways in which the *cis*-cation can be neutralized, we find first that simple loss of a proton yields (IX), R = H_2, which fits the known facts for the sesquiterpene, humulene, and suggests the *cis* and *trans* orientation of the double bonds as well, the models indicating clearly a *trans* double bond at C_{9-10} as shown. The ketone (IX), R = O, is thus zerumbone, with the same *cis-trans-trans* geometry predicted for the double bonds. The *cis*-cation can also be neutralized by attack of a double bond on the C_{10} cation; the conformation of (VIa) allows this *only* with the Δ^{2-3} double bond (the Δ^{6-7} bond is blocked by the "inside" hydrogen at C_1) and a

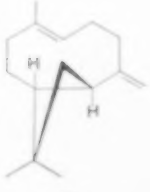


IIIa

VIa

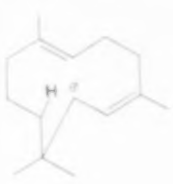


IX

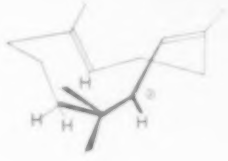


X

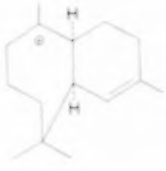
concerted loss of hydrogen from the C_3-methyl group yields carophyllene (X) directly, its known stereochemistry (*trans*-fused four-membered ring and *trans* double bond at C_{6-7}) a direct consequence of the conformation of (VI). Finally, the "inside" hydrogen at C_1 can undergo a 1,3-migration* to relieve its strain, yielding the ion (XI). The conformation of (XI), depicted in (XIa), is such as to provide considerable overlap of the π-electrons at C_6 with those of the allylic carbonium ion at C_1, so that collapse to the *cis*-fused bicyclic ion (XII) will be facile. The geometry of (XII) is such that C_7 is close to the double bond at C_2–C_3; although the electronic preference would now dictate the formation of a C_2–C_7 bond, this process would yield a highly strained four-membered ring in a polycyclic system. Hence we may reasonably expect instead



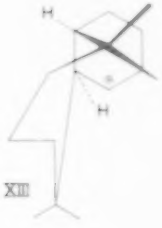
XI



XIa



XII

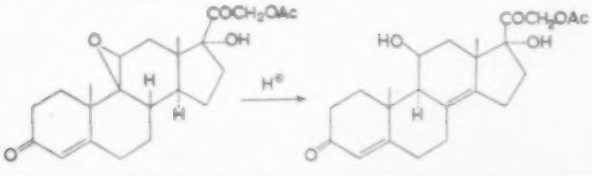


XIII

XIV

XV

* Migrations of this sort are known in rigid systems, cf. the familiar cases in the [2,2,1]-bicycloheptane series[5] and the steroid case of Wendler,[6] given below. The rigidity of (VI) and the close proximity of the involved atoms therein strongly suggest it as a comparable example.

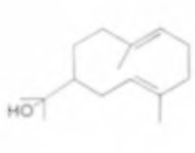


[5] J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *J. Amer. Chem. Soc.* **76**, 4501 (1954), and references therein.

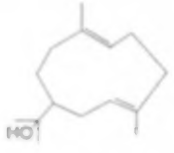
[6] N. L. Wendler, R. P. Graber, C. S. Snoddy, Jr. and F. W. Bollinger, *J. Amer. Chem. Soc.* **79**, 4476 (1957).

a cyclization to the ion (XIII), which, rewritten as (XIV), will be recognized as a [2,2,1]-bicycloheptane derivative capable of neutralizing the cation by rearrangement and deprotonation to the sesquiterpene, longifolene (XV). Thus the conformation of (VI) can be seen to proceed uniquely to these complex substances in all stereochemical detail. It should be remarked that caryophyllene and humulene occur together in *Eugenia caryophyllata* and that caryophyllene and longifolene are the only sesquiterpenes known to date to be found in pines (*Pinus* spp.).[4]

Models of the *trans*-cation (VII) reveal that the two-double bonds are extremely close to each other, by contrast with (VI), and that there are no "inside" hydrogens. The cationic center now resides out on the pendent isopropyl group where it may be hydrated or suffer the further extensive oxidation characteristic of the sesquiterpene lactones, all of which can be shown to derive from (VII). Taking simple hydration as an example of the fate of the *trans*-cation, let us examine the resultant alcohol, of which the various pictorializations (XVIa–d) are entirely equivalent. It will be seen at once that this alcohol (XVI) possesses two double bonds uniquely situated for concerted cyclizations, with complete *trans* anti-parallel additions to the double bonds, to yield the bicyclic products (XVIIa,b) and (XVIIIa,b) with R═H for a simple acid-catalyzed cyclization or R═OH for an oxidative cyclization reminiscent of those in the triterpene series. As the geometry of such a concerted cyclization requires,



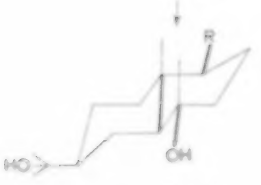
XVIa



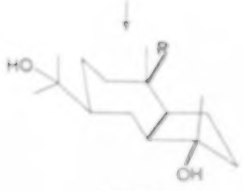
XVIb

XVIc

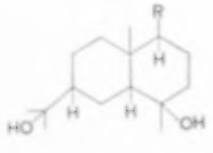
XVId



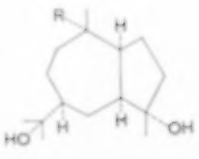
XVIIa



XVIIIa



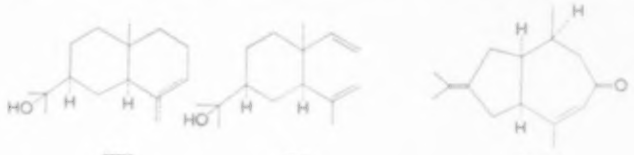
XVIIb



XVIIIb

all the new bonds formed are parallel, as indicated by the heavier lines in (XVIIa) and (XVIIIa). The product (XVII) derives from a completely Markownikoff-oriented polarization of the two double bonds, whereas one double bond must polarize in an anti-Markownikoff fashion for the production of (XVIII), a situation akin to the C-ring cyclization of lanosterol from squalene[2] and allowable here because of the compelling proximity of the double bonds.

Product (XVII) is the direct precursor of eudesmol (XIX) and the other sesquiterpenes of that skeleton (santonin, cyperone, etc.) and is in complete accord with the stereochemistry of that group in all cases in which this is known. Furthermore, a direct six-membered-ring cycling of the electrons in (XVIa) yields elemol (XX). Product (XVIII) is the precursor of the large body of sequiterpenes with the guaiazulene skeleton and predicts their stereochemistry, although this is not at present known for any example. Alternatively, a simple double bond isomerization from (XVIc)

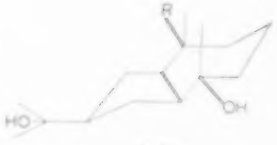


XIX XX XXIV

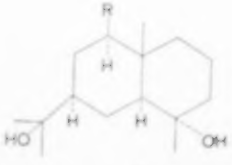
to (XXI) can occur with negligible steric complaint, followed by entirely analogous cyclizations to (XXa,b) and (XXIIIa, b). It is tempting to consider the possibility that since this involves an extra biogenetic step, fewer sesquiterpenes will arise by this route. This seems to be borne out by the examples presently known: (XXIII)

XXI

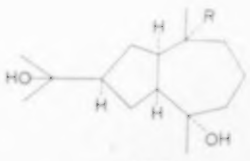
XXIIa



XXIIIa

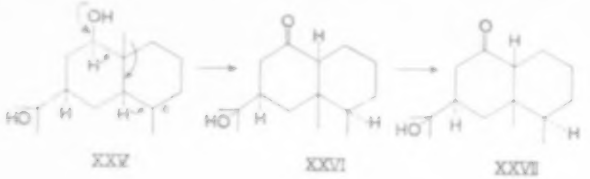


XXIIb

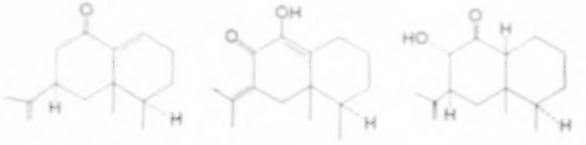


XXIIIb

represents the known stereochemistry of β-vetivone (XXIV) and presumably yields the few other vetivazulene skeletons in nature, whereas (XXII) yields only the eremophilones, by the following means. (XXII) is considered as (XXV) (oxidative cyclization) which reveals the ideal anti-parallel geometry for a multi-group rearrangement (indicated by arrows) of the sort so dramatically exemplified in friedelin chemistry.[7] Such a migration yields (XXVI), which may isomerize to the more stable ketone (XXVII). This in turn, by side-chain dehydration as well as oxidation of either enol, yields eremophilone (XXVIII), hydroxy-eremophilone (XXIX), and hydroxydihydro-eremophilone (XXX), all three of which are found to co-exist in nature; the stereochemisty of (XXX) is known to be as indicated.

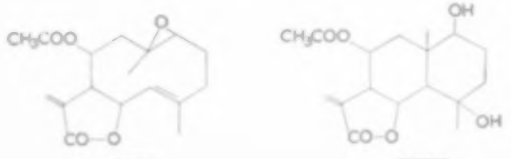


XXV XXVI XXVII



XXVIII XXIX XXX

Finally, we might reasonably expect examples of uncyclized (VII) to be found in natural sources; such monocyclic sesquiterpenes would be predicted to undergo facile cyclizations *in vitro* of the sort postulated here for biogenesis, to bicyclic derivatives of (XVII) and (XVIII). This expectation has recently been realized. Thus, pyrethrosin has been shown to possess structure (XXXI) and to cyclize under a variety of acidic conditions to give such products as (XXXII). Two other sesquiter-



XXXI XXXII

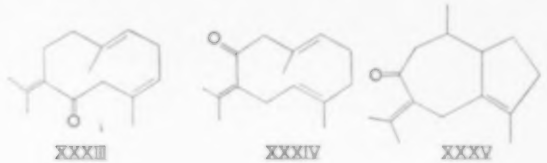
penes, unequivocably monocyclic, deserve attention here. The first is germacrone, said to possess structure (XXXIII).[8] The biogenetic hypothesis outlined here dictates (XXXIV) as the simplest structure for germacrone consistent with the experimental evidence. In accord with the views developed above, this accommodates readily the observation of Treibs[9] that germacrone yields (XXXV) on acid catalysis and

[7] E. J. Corey and J. J. Ursprung, *J. Amer. Chem. Soc.* **78,** 5041 (1956).

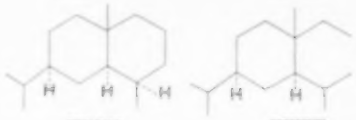
[8] I. Ognjanoff, D. Ivanoff, V. Herout, M. Horák, J. Pliva and F. Sorm, *Chem. & Ind.* 820 (1957); *Coll. Czech. Chem. Comm.* **23,** 2033 (1958); V. Herout and M. Suchy, *Ibid.* **23,** 2169 (1958); M. Suchy and F. Sorm, *Ibid.* **23,** 2175 (1958).

[9] W. Treibs, *Liebigs Ann.* **576,** 116 (1952).

the obtention[8] of selinane (XXXVI) on catalytic hydrogenation, in acid, of the alcohol corresponding to germacrone. Of similar interest is the observation that dehydration of the latter alcohol followed by hydrogenation yields elemane (XXXVII).



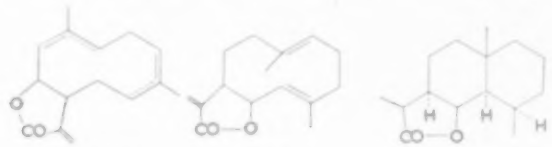
XXXIII XXXIV XXXV



XXXVI XXXVII

VOL. 7 1959

Both pyrethrosin and germacrone afford cham- or guaiazulene on dehydrogenation, as does the final example, costunolide, recently formulated as (XXXVIII).[10] The hypothesis implies instead the structure (XXXIX). Costunolide yields on catalytic



XXXVIII XXXIX XL

hydrogenation in acid a saturated tetrahydro-lactone, m.p. 154°, which we would formulate as (XL), analogous to (XVII) above. The lactone (XL) is in fact the structure of tetrahydrodeoxy-santonin, which is known to possess m.p. 153–154°. These examples will serve to indicate the utility of the hypothesis in considerations of sesquiterpene structures.

Note added in proof: The absolute stereochemistry is in fact enantiomeric with the structures drawn here, in those cases in which this is known.

[10] A. Somasekar Rao, G. R. Kelkar and S. C. Bhattacharyya, *Chem. & Ind.* 1359 (1958).

Tetrahedron, 1959, Vol. 7, pp. 90 to 103. Pergamon Press Ltd. Printed in Northern Ireland

STRUCTURE MOLECULAIRE ET ACTIVITE OESTROGENE—XVII*

COMPARAISON DES CONFIGURATIONS ABSOLUES DES ACIDES BISDEHYDRODOISYNOLIQUE NORMAL ET α, α-DIMETHYL β-ETHYL ALLENOLIQUE PHYSIOLOGIQUEMENT ACTIFS

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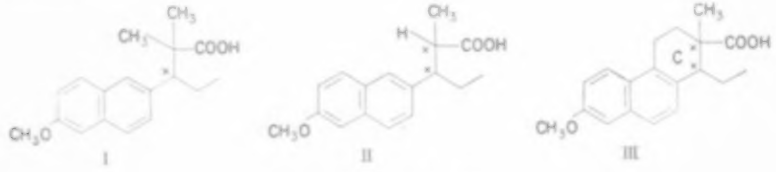
Résumé—Les configurations des acides fortement oestrogènes: acide α,α-diméthyl β-éthyl allénolique *gauche* et acide *n*-bisdéhydrodoisynolique *gauche* ont été déterminées comparativement.

Abstract—A stereochemical correlation has been established between the two highly estrogenic acids: levorotatory α,α-diméthyl β-éthyl allenolic acid (I) and levorotatory *n*-bisdehydrodoisynolic acid (III). The configuration of the corresponding asymmetric centre is *opposite* in these compounds.

ON sait que l'acide bisdéhydrodoisynolique III se présente sous la forme de deux racémiques dûs à la présence de deux atomes de carbone asymétrique en 1 et 2. L'un d'eux, dit *normal* possède, par rapport au cycle C, les groupements carboxyle et éthyle en position *cis*. Cet acide peut être dédoublé en ses antipodes et, seul, le produit *gauche* (obtenu également dans la fusion alcaline de l'équilénine naturelle) est physiologiquement actif (activité 0,5 γ†). Le second acide racémique appelé "Iso", qui possède les groupements carboxyle et éthyle en position *trans*, est physiologiquement inactif.



Mélange de X et XI

Par ailleurs, un des représentants les plus actifs de la série "allénolique",[2] l'acide

* XVI voir référence 2h.

† Activités mesurées pour les deux acides dans les mêmes conditions par le professeur R. Courrier.

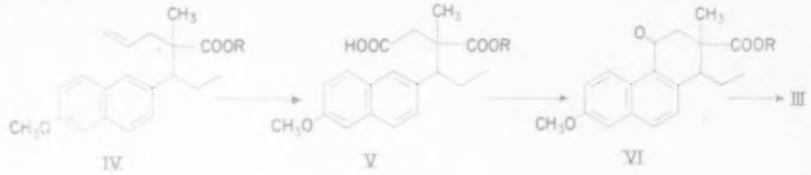
[1a] K. Miescher, *Helv. Chim. Acta* **27**, 1727 (1944); [b] J. Heer, Billeter et K. Miescher, *Ibid.* **28**, 991 (1945); [c] *Ibid.* **28**, 1342 (1945); [d] G. Anner et K. Miescher, *Ibid.* **29**, 586 (1946); [e] J. Heer et K. Miescher, *Ibid.* **29**, 1895 (1946); [f] K. Miescher, *Chem. Rev.* **43**, 367 (1948).

[2a] R. Courrier, A. Horeau et J. Jacques, *C. R. Soc. Biol.* **141**, 159 (1947); [b] *C. R. Acad. Sci., Paris* **224**, 1401 (1947); [c] A. Horeau et J. Jacques, *Ibid.* **224**, 862 (1947); [d] A. Horeau, J. Jacques et S. Julia, *Ibid.* **227**, 1278 (1948); [e] J. Jacques et A. Horeau, *Bull. Soc. Chim. Fr.* **15**, 711 (1948); [f] *Ibid.* **17**, 512 (1950); [g] R. Courrier, A. Horeau et J. Jacques, *C. R. Acad. Sci., Paris* **232**, 2382 (1951); [h] A. Ormancey et A. Horeau, *Bull. Soc. Chim. Fr.* 962 (1955); [i] A. Horeau, R. Gay et R. Courrier, *C. R. Acad. Sci., Paris* **242**, 429 (1956); [j] R. Courrier, A. Horeau, J. Jacques et R. Gay, *Ibid.* **238**, 2476 (1954).

α,α-diméthyl β-éthyl allénolique I, a pu être dédoublé en ses antipodes.[3] L'acide gauche est le plus actif physiologiquement (activité 1,5 γ) bien que l'antipode droit possède encore le cinquième de cette activité.*

Il était intéressant, dans le cadre de l'étude générale que nous poursuivons sur les rapports entre la structure moléculaire et le pouvoir oestrogène, de comparer les configurations absolues des acides physiologiquement actifs dans ces deux séries différentes.

Cette comparaison est, en effet, possible grâce à la synthèse que l'un de nous a déjà décrite brièvement[4] et qui permet le passage de la série allénolique à la série doisynolique.

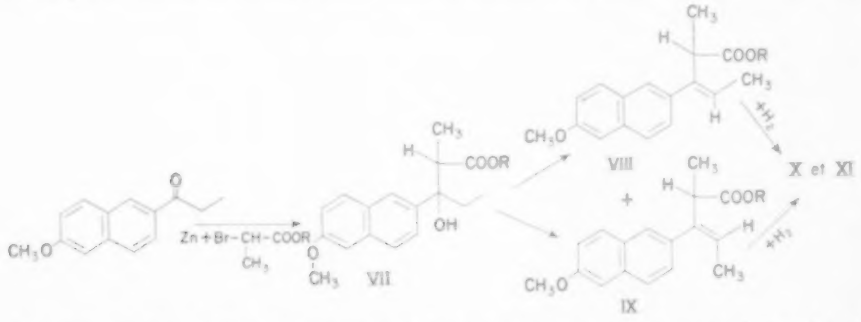


L'ester méthylique de l'acide racémique II, est transformable, soit: 1° par sodation suivie de méthylation et de saponification, en acide α,α-diméthyl β-éthyl allénolique I, soit: 2° par sodation suivie d'allylation, en acide bisdéhydrodoisynolique *normal* racémique, en passant par les intermédiaires suivants dérivé allylé IV, acide ester V, γ-céto ester VI et acide final III.

Dans les mêmes conditions l'ester méthylique de l'acide *lévogyre* Xg (R = H) conduit d'une part à l'acide diméthyléthylallénolique *lévogyre* XIIg (R = H), et d'autre part à l'acide (+)n-bisdéhydrodoisynolique XVIId, en passant par l'ester α-allylé XIVg (voir Tableaux A et B).

Voici quelques détails sur ces réactions qui établissent la filiation entre les acides des deux séries:

L'action suivant Réformatsky de l'α-bromopropionate d'éthyle en présence de zinc, sur le méthoxy-2 propionyl-6 naphtalène, fournit un carbinol VII, qui peut être déshydraté, hydrogéné et saponifié en un mélange d'acides α-méthyl β-éthyl allénolique isomères X et XI, précédemment décrits par l'un de nous avec Jacques.[5]



* Cette activité peut être due à une "racémisation" dans l'organisme beaucoup plus facile qu'en série doisynolique, où la molécule possède deux atomes de carbone asymétrique.

[3] J. Jacques et A. Horeau, *Bull. Soc. Chim. Fr.* **16**, 301 (1949).

[4] R. Gay, *C. R. Acad. Sci., Paris* **242**, 3084 (1956); Thèse Doctorat d'Etat. Faculté des Sciences de Paris (en impression aux *Annales de Chimie*).

[5] A. Horeau et J. Jacques, *Bull. Soc. Chim. Fr.* **15**, 707 (1948).

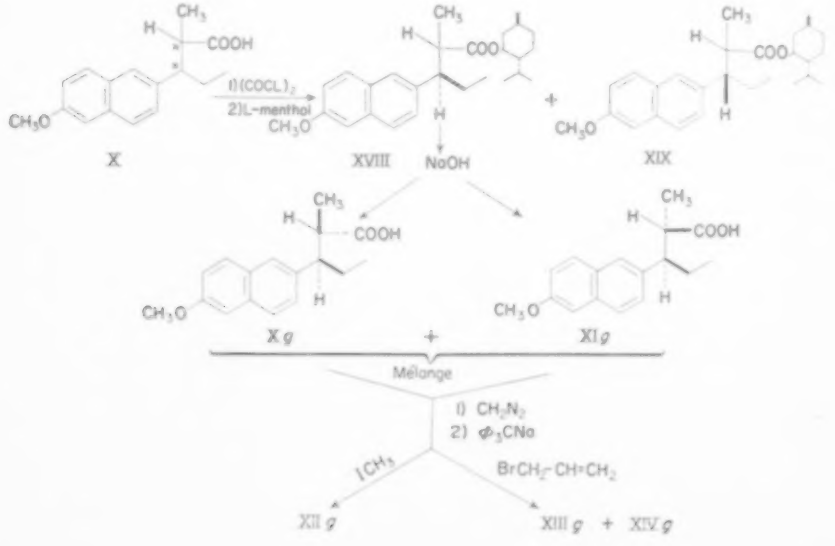
L'un de ces acides racémiques X (R = H) fond à 110°, l'autre XI (R = H), à 137°. Ils peuvent être séparés par chromatographie sur alumine du mélange de leur ester méthylique, suivie de saponification. Cependant, Lam-Chanh-Binh et Jacques[6] ont étudié les produits éthyléniques VIII et IX résultant de la déshydratation du carbinol VII et défini des conditions précises d'hydrogénation permettant l'obtention à volonté et de manière pratique, de mélanges riches en chacun des acides X (R = H) et XI (R = H), mélanges à partir desquels les acides eux-mêmes peuvent être obtenus à l'état de pureté par recristallisation.

L'acide X (R = H) F. 109° (Tableau A), peut être dédoublé en ses antipodes, Xg (R = H) et Xd (R = H), F. 98°, $[\alpha]_D^{20} \pm 23°$. La quinine permet l'isolement de l'acide gauche; et les eaux-mères du sel de quinine de cet acide gauche fournissent, par acidification et extraction à l'éther, un mélange riche en isomère droit qui est purifié par l'intermédiaire du sel d'éphédrine gauche.

L'acide XI (R = H), F. 137°, peut être dédoublé en ses antipodes XIg (R = H) et XId (R = H) par un procédé identique, F. 133°, $[\alpha]_D^{20} \pm 5°$.

L'acide Xg (R = H) est transformé en ester méthylique par traitement au diazométhane, et l'action d'une solution éthérée de triphénylméthyl-sodium sur cet ester (voir Tableau A) suivie de l'action de l'iodure de méthyle, conduit, après saponification de l'ester obtenu, à l'acide α,α-diméthyl β-éthylallénolique gauche XIIg (R = H). F. 142°, $[\alpha]_D^{22} -23°$, identique au produit de Jacques et Horeau.[3] Nous avons vérifié que, dans les mêmes conditions, l'acide Xd conduit à l'acide α,α-diméthyl β-éthylallénolique droit XIId (R = H). Par ailleurs, l'acide XIg conduit à l'acide α,α-diméthyl β-éthylallénolique gauche XIIg (R = H).

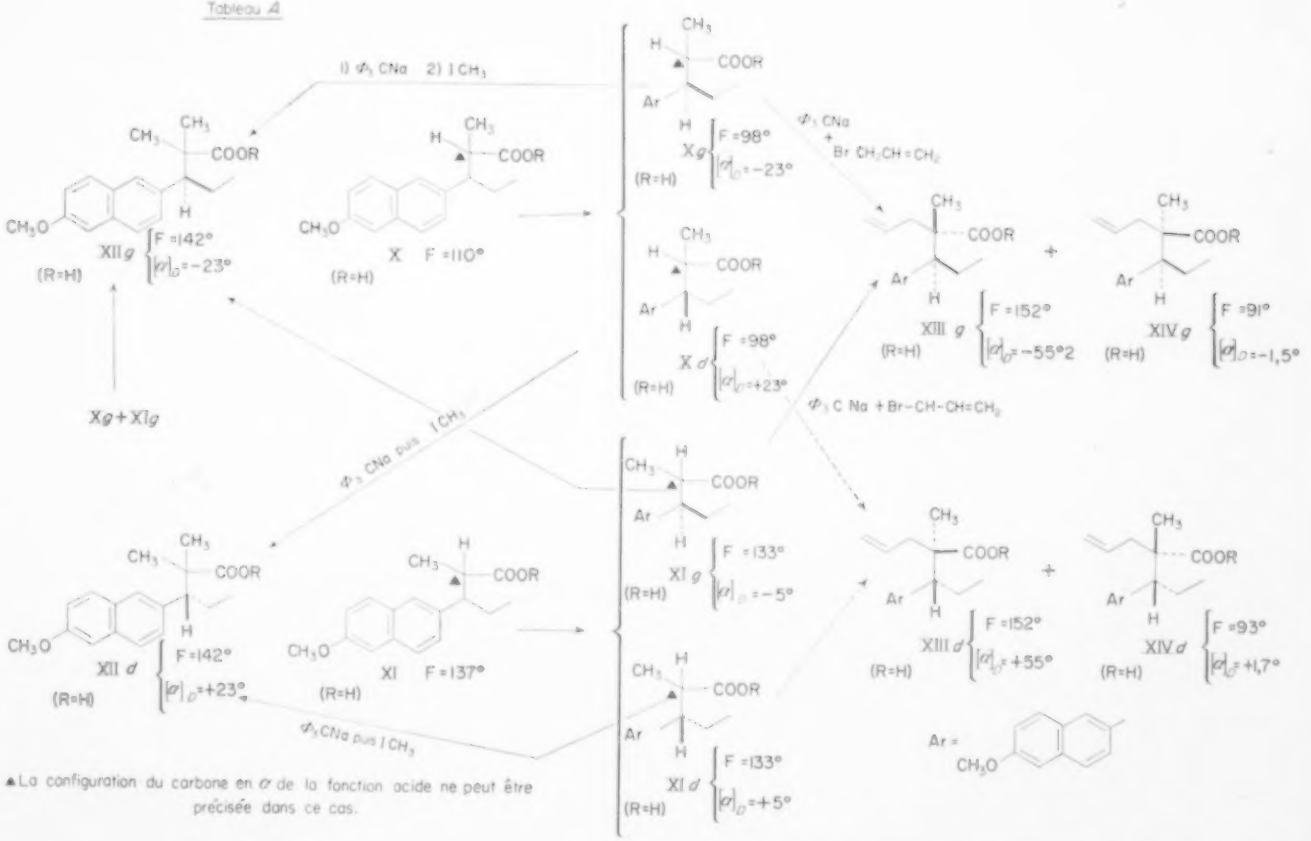
Le dédoublement de l'acide α-méthyl β-éthylallénolique X (R = H), F. 109–110°, peut aussi s'effectuer par l'intermédiaire des esters *l*-menthyliques facilement accessibles, à partir du chlorure d'acide chauffé sous azote à 60° avec du *l*-menthol.



[6] Lam-Chanh-Binh et J. Jacques, en impression.

VOL. 7 1959

Tableau A



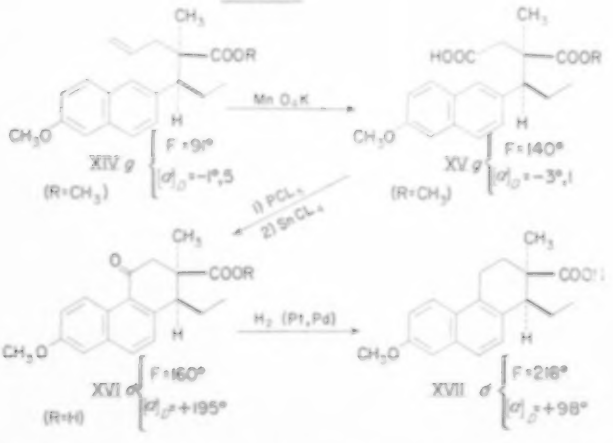
▲La configuration du carbone en α de la fonction acide ne peut être précisée dans ce cas.

On sépare par cristallisation fractionnée dans le méthanol, les esters *l*-menthyliques des deux antipodes, soit XVIII, F. 136°, $[\alpha]_D^{20}$ −74,2° et XIX, F. 76°, $[\alpha]_D^{22}$ −6,8°. Cependant, le retour aux acides libres par la saponification, qui est difficile et s'effectue à température élevée, s'accompagne d'une épimérisation du carbone en α de la fonction acide et on obtient un mélange des deux acides diastéréoisomères Xg (R = H) et XIg (R = H) $[\alpha]_D^{20}$ −16,7°. Ce fait n'oblige pas à rejeter l'emploi du *l*-menthol pour le dédoublement car celui-ci est complet: en effet la méthylation des esters méthyliques du mélange d'acides brut par le brocédé décrit plus haut conduit à un acide α,α-diméthyl β-allénolique gauche très pur et, pour les opérations ultérieures, il importe seulement d'avoir en β de la fonction acide une configuration unique et déterminée. Par ailleurs, l'alcoylation des esters purs Xg (R = CH_3) ou XIg (R = CH_3), par l'action du triphénylméthyl–sodium et d'un halogénure d'alcoyle conduit, comme nous l'avons déjà montré sur les esters racémiques[7] dont ils dérivent, aux mélanges des deux esters α-alcoylés diastéréoisomères possibles (quand le radical alcoyle introduit est autre que CH_3). Ainsi l'allylation a-t-elle été effectuée après estérification soit à partir de l'acide Xg (R = H) pur, soit à partir de mélange des acides Xg (R = H) et XIg (R = H).

Dans les deux cas on obtient le mélange des deux acides α-allylés diastéréoisomères XIIIg (R = H), F. 150–152°.* $[\alpha]_D^{20}$ −55,2° et XIVg (R = H), F. 90–91° $[\alpha]_D^{20}$ −1,5°. Ces acides sont obtenus à l'état de pureté en saponifiant leurs esters méthyliques séparés par chromatographie sur alumine: XIIIg (R = CH_3), F. 45–47° et XIVg (R = CH_3), F. 53–55°.

Les configurations spatiales de ces acides (malgré l'épimérisation signalée pour le carbone en α de la fonction acide) peuvent être précisées telles qu'elles figurent sur les schémas puisque, par exemple, par une suite de transformations ultérieures (Tableau B), l'acide XIVg (R = H) fournit un acide bisdéhydrodoisynolique de la série "*normale*".†

Tableau B



* Les antipodes optiques de ces acides ont été obtenus parallèlement et par un procédé identique à partir des acides XIIId et XIVd.

† L'un de nous a montré[8] que les acides racémiques XIV et XIII conduisaient par cette même série de transformation respectivement aux acides bisdéhydrodoisynoliques racémiques *Iso* et *Normal*.

[7] R. Gay et A. Horeau, *Bull. Soc. Chim. Fr.* **955** (1955).

L'action d'une quantité calculée de permanganate de potassium en solution acétonique et en présence de sulfate de magnésium sur l'ester XIVg ($R = CH_3$) fournit l'acide-ester XVg ($R = CH_3$); celui-ci est purifié par l'intermédiaire de son diester méthylique que l'on soumet à une saponification sélective par de la baryte.

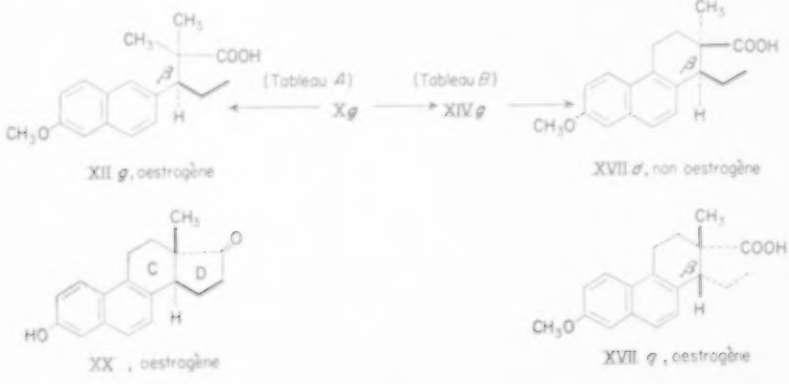
L'acide-ester XVg ($R = CH_3$) ainsi purifié conduit au céto-ester XVId ($R = CH_3$) par l'action, en solution benzénique, du pentachlorure de phosphore (le chlorure d'acide ainsi préparé n'est pas isolé) et traitement par le chlorure stannique. Ce mode opératoire a déjà été décrit par Johnson et ses collaborateurs dans un cas voisin.[8]

L'ester cétonique (non obtenu cristallisé) conduit par saponification à l'acide cétonique XVId ($R = H$), F. 159–160° $[\alpha]_D^{19}$ +195°. On obtient alors, l'acide final XVIId, à partir de cet acide cétonique par hydrogénation catalytique en présence de platine palladié suivant la méthode de Zélinsky–Packendorff.[9]

Fait remarquable: cet acide XVIId, F. 218°, est l'acide n-bisdéhydrodoisynolique dextrogyre $[\alpha]_D^{20}$ +98°.[10] Ce résultat est confirmé par l'examen du point de fusion des mélanges de cet acide et des acides authentiques méthyl-7 n-bisdéhydrodoisynolique *droit* et *gauche*.[9] (Voir fin de la partie expérimentale).

Conclusion

L'acide α-méthyl β-éthylallénolique Xg gauche conduit d'une part par méthylation à l'acide α,α-diméthyl β-éthylallénolique *gauche* XIIg, physiologiquement actif et, d'autre part, par la suite de réaction indiquées ci-dessus à l'acide n-bisdéhydrodoisynolique *droit* XVIId physiologiquement inactif. Seul l'antipode XVIIg est fortement oestrogène.[1,10]



Dans les deux séries fortement oestrogènes, l'activité physiologique est donc conditionnée par une configuration inversée du carbone situé en β de la fonction acide.

On peut cependant remarquer que dans les hormones oestrogènes naturelles la jonction des cycles C et D est *trans*; c'est le cas de la *d*-équilénine naturelle XX

[8] Echantillons que nous devons à l'amabilité de Messieurs Wettstein et Anner que nous remercions très vivement.

[8] D. L. Turner, B. K. Bhattacharyya, R. P. Graber et W. S. Johnson, *J. Amer. Chem. Soc.* **72**, 5656 (1950).

[9] Zelinsky, Packendorff et Leder Packendorff, *Ber.* **66**, 872 (1933); **67**, 300 (1934). Voir également les références citées en.[8]

[10] R. Rometsch et K. Miescher, *Helv. Chim. Acta* **29**, 1231 (1946).

oestrogène. L'activité de l'acide n-bisdéhydrodoisynolique XVIIg, obtenu par fusion alcaline de l'équilénine est liée a une épimérisation portant sur le carbone β de la fonction carboxyle ainsi que l'ont fait remarquer Heer et Miescher.[1e]

Ainsi donc l'acide α,α-diméthyl β-éthylallénolique le plus oestrogène c'est-à-dire le gauche XIIg à la configuration "naturelle" contrairement à l'acide n-bisdéhydrodoisynolique XVIIg physiologiquement le plus actif.

PARTIE EXPERIMENTALE

Acides méthyl-2 (méthoxy-6' naphtyl-2')-3 pentanoïques X (R = H) *et* XI (R = H)

La méthode la plus pratique d'obtention des acides racémiques purs est celle décrite par Lam-Chanh-Binh et Jacques,[6] mais la séparation des deux acides racémiques XI F. 137° et X F. 110°, à partir de leur mélange obtenu par synthèse,[5] peut s'effectuer par cristallisations fractionnées ou plus aisément par chromatographie de leurs esters méthyliques. Exemple: Un mélange de 3,0 g d'esters méthyliques est chromatographié sur Alumine Merck (activité IV). L'hexane élue en tête de colonne 0,100 g d'ester méthylique XI (R = CH_3), F. 45–46°, qui, par saponification, fournit l'acide F. 137° XI (R = H). Les mélanges d'hexane et de cyclohexane en proportions variables éluent des fractions d'esters dont la teneur en second racémique va croissante. Le mélange cyclohexane–benzène (3/1) élue 0,8 g du second ester racémique X (R = CH_3), F. 61–63°. Par saponification, on obtient l'acide X (R = H) F. 109–110°.

Acide méthyl-2 (méthoxy-6' naphtyl-2')-3 pentanoïque Xg (R = H). *Dédoublement de l'acide racémique* X (R = H) F. 109°

On met en solution rapidement dans 50 cm³ d'éthanol ordinaire, 2,74 g d'acide X (R = H) F. 108–110° et 3,24 g de quinine, F. 166–168°. La solution homogène laisse déposer presque immédiatement des cristaux de sel de quinine; on laisse reposer une nuit et, après filtration et lavage avec 15 cm³ d'éthanol on obtient 2,7 g de produit brut.

Ce produit est recristallisé trois fois successivement par dissolution à chaud dans l'éthanol et lavage sur filtre. Les poids recueillis sont respectivement de 2 g, 1,25 g (à partir de 1,7 g) et 0,6 g (à partir de 0,7 g), les pouvoirs rotatoires des acides correspondants sont de $[\alpha]_D^{20}$ −17,2°, −22,2° et −22,8° (éthanol absolu). Ces acides sont obtenus à partir d'une fraction des sels de quinine (comme il est indiqué quelques lignes plus loin) prélevée avant chaque recristallisation.

On obtient donc facilement 0,6 g de sel de quinine. Ce sel est agité dans l'éther en présence d'acide chlorhydrique; après dissolution totale et séparation de la solution aqueuse de chlorhydrate de quinine, l'éther abandonne 0,260 g d'acide brut qui est recristallisé dans le méthanol aqueux. F. 96–98°.

$[\alpha]_D^{20}$ −22,8° ± 1° (0,1974 g dans 20 cm³ alcool absolu.). (Analyse: $C_{17}H_{20}O_3$ (272,3) Calc: C, 74,97; H, 7,40; Tr: C, 74,73; H, 7,24%)

Acide méthyl-2 (méthoxy-6'naphtyl-2')-3 pentanoïque Xd (R = H)

Les eaux-mères des 2,7 g de sel de quinine brut précédent sont acidifiées par l'acide chlorhydrique et l'extraction à l'éther fournit 1,55 g d'acide impur.

Cet acide en solution dans 20 cm³ d'alcool éthylique est traité par 1,1 g d'éphédrine gauche; on ajoute ensuite 20 cm³ d'eau distillée. Le sel d'éphédrine cristallise, on laisse une nuit au repos, filtre, lave avec 5 cm³ d'un mélange éthanol–eau 1/1, et recueille 1,35 g de cristaux. Ceux-ci sont recristallisés dans 20 cm³ d'éthanol–eau 1/1. Après filtration, lavage par 2,5 cm³ (éthanol–eau), on obtient 1,1 g de cristaux A_1 ce sel 0,450 g fournit, après traitement par l'acide chlorhydrique, 0,261 g d'acide $[\alpha]_D^{20}$ +24,1°. Le dédoublement est déjà complet ainsi que le montre la purification suivante: le reste des cristaux, soit 0,650 g, est recristallisé dans 10 cm³ du mélange alcool–eau (1/1). Après filtration et lavage (par 3 cm³ du mélange hydro-alcoolique), les cristaux A_2 obtenus sont traités par l'acide chlorhydrique. L'acide brut, recristallisé dans le méthanol aqueux, fournit 0,230 g d'acide F. 98–99°. (Analyse: $C_{17}H_{20}O_3$ (272,3) Calc: C, 74,97; H, 7,40; Tr: C, 75,07; H, 7,41%). $[\alpha]_D^{20}$ +23,5° ± 1° (0,2191 g dans 20 cm³ d'éthanol absolu).

Acide méthyl-2 (méthoxy-6' naphtyl-2')-3 pentanoïque XIg (R = H). *Dédoublement de l'acide racémique* XI (R = H) F. 137°

2,75 g d'acide XI (R = H) F. 137° et 3,3 g de quinine sont dissous dans 28 cm³ d'alcool éthylique à 95°. On dilue par 25 cm³ d'eau distillée. On chauffe à reflux jusqu'à dissolution complète des cristaux formés. Après refroidissement et repos, on filtre le sel de quinine et lave avec 9 cm³ d'un mélange hydro-alcoolique (4 cm³ d'alcool et 5 cm³ d'eau). On obtient 3,55 g de cristaux B. On recristallise à trois reprises ce produit dans dix fois son poids d'alcool aqueux (5 : 4) et lave sur filtre avec un peu de ce mélange. Le sel de quinine est détruit par l'acide chlorhydrique en solution éthérée. La solution éthérée, après lavage à l'eau, séchage et évaporation, fournit un acide brut, qui, après recristallisation dans le méthanol aqueux (8 cm³ méthanol et 3,5 cm³ d'eau) donne 1 g d'acide F. 133–134°.

(Analyse: $C_{17}H_{20}O_3$ (272,3) Calc: C, 74,97; H, 7,40; Tr: C, 75,06; H, 7,45%).
$[\alpha]_D^{20}$ −4,9 ± 1° (0,2257 g dans 20 cm³ d'éthanol absolu).

Acide methyl-2 (methoxy-6' naphtyl-2')-3 pentanoïque XId (R = H)

Les eaux-mères B du premier sel de quinine de l'acide précédent sont concentrées et traitées par l'acide chlorhydrique en solution éthérée; ce traitement fournit 1,1 g d'acide impur.

Cet acide en solution dans 13 cm³ d'alcool est traité par 0,8 g d'éphédrine gauche. On ajoute alors lentement 17 cm³ d'eau distillée. Après cristallisation, repos, filtration et lavage, on obtient 1,05 g de sel d'éphédrine. Celui-ci recristallisé dans 6,5 cm³ d'alcool et 8,5 cm³ d'eau donne, après filtration et lavage, 0,850 g de cristaux.

Le sel d'éphédrine détruit par l'acide chlorhydrique en solution éthérée fournit 0,450 g d'acide, F. 129–130°. Un échantillon, après recristallisation dans le méthanol aqueux, fond à 132–133°.
(Analyse: $C_{17}H_{20}O_3$ (272,3) Calc: C, 74,97; H, 7,40; Tr: C, 75,09; H, 7,60%).
$[\alpha]_D^{20}$ −5° ± 1° (0,2377 g dans 20 cm³ d'éthanol absolu).

Acide diméthyl-2.2 (méthoxy-6' naphtyl-2')-3 pentanoïque XIIg (R = H)

L'acide Xg, F. 98–100° $[\alpha]_D$ −22,8°, (0,4 g) est soumis à l'action du diazométhane et l'ester ainsi obtenu est dissous avec agitation sous atmosphère d'azote dans 25 cm³ d'une solution éthérée de triphénylméthyl-sodium 0,135 N. Après un contact de 40 cm on introduit en une seule fois et sous agitation 2,5 cm³ d'iodure de méthyle.

La solution éthérée de triphénylméthyl-sodium vire instantanément du rouge au jaune alors que l'iodure de sodium précipite. On laisse ainsi plusieurs heures au repos. On lave la phase éthérée à l'eau, sèche sur sulfate de sodium puis chasse le solvant. Le produit brut de la réaction est saponifié par chauffage à l'ébullition pendant 45 mn avec 5 cm³ de lessive de soude 10 N et 25 cm³ de méthoxy-éthanol. Après refroidissement on reprend par l'eau, épuise à l'éther, précipite la solution sodique par l'acide chlorhydrique dilué et on recueille ainsi un produit brut qui, après recristallisation du méthanol aqueux, fournit 210 mg d'acide lévogyre XIIg (R = H), F. 141–142°. $[\alpha]_D^{22}$ −23° ± 1,5° (0,1496 g dans 20 cm³ d'alcool absolu). Cet acide est identique à celui obtenu précédemment par Horeau et Jacques.[3]

Acide diméthyl-2.2 (méthoxy-6' naphtyl-2')-3 pentanoïque XIId (R = H)

0,4 g d'acide Xd (R = H), F. 98–100° $[\alpha]_D^{20}$ +23,5° sont estérifiés par le diazométhane. L'ester méthylique est traité comme précédemment par le triphénylméthyl-sodium puis par l'iodure de méthyle. Le produit brut de l'alcoylation après saponification et recristallisation fournit 0,200 g d'acide XIId (R = H), F. 142–143° $[\alpha]_D^{20}$ +23° ± 1,5° (0,152 g dans 20 cm³ d'éthanol absolu).

Cet acide est identique à l'acide dextrogyre préparé précédemment par Horeau et Jacques.[3]

Acide dimethyl-2.2 (methoxy-6' naphtyl-2')-3 pentanoïque XIIg (R = H)
(opération conduite comme précédemment).

0,260 g d'acide XIg F. 131–134° $[\alpha]_D$ −4,9° sont estérifiés par le diazométhane. L'ester est dissous par agitation et sous atmosphère d'azote dans 15 cm³ de solution éthérée de triphénylméthyl-sodium (0,135 N). Après un contact de 45 mn on introduit en une seule fois 2 cm³ d'iodure de méthyle. On laisse en contact deux heures.

Le produit brut de l'alcoylation fournit après saponification et recristallisation 0,130 g d'acide XIIg (R = H), F. 142–143° $[\alpha]_D^{20}$ −25° (±2°). (0,128 g dans 20 cm³ d'éthanol absolu).

VOL. 7 1959

Méthyl-2 (méthoxy-6' naphtyl-2')-3 pentanoate de l-menthyle XVIII et XIX
(Esters *l*-menthyliques de l'acide X (R = H).

Préparation du chlorure de l'acide racémique X (R = H). 2,74 g (1/100 mol) d'acide X (R = H), F. 109–110°, sont dissous dans 15 cm³ de benzène anhydre dans un récipient muni d'une garde au chlorure de calcium. On refroidit dans la glace et on introduit en une seule fois 2 cm³ de chlorure d'oxalyle fraichement distillé. La solution se teinte en orange des bulles se dégagent. Le mélange est maintenu à 0° dans la glace pendant deux heures, puis à la température ordinaire une nuit. L'excès de chlorure d'oxalyle est chassé par distillation à 60° sous vide et cette élimination est complètée par deux additions de benzène que l'on élimine sous pression réduite à une température ne dépassant pas 60°.

Préparation des esters l-menthyliques XVIII *et* XIX. Après refroidissement on ajoute 1,56 g de *l*-menthol. On porte à 60° sous atmosphère d'azote; la réaction s'amorce aussitôt. On maintient cette température pendant une heure; le dégagement d'acide chlorhydrique a alors beaucoup ralenti et on ajoute à nouveau 0,150 g de *l*-menthol (10% d'excès) puis on porte progressivement le mélange réactionnel à 100° température que l'on maintient une demi-heure, puis on laisse refroidir sous azote.

Séparation des esters l-menthyliques XVIII *et* XIX. Le produit brut précédent est repris par 45 cm³ de méthanol ce qui provoque une cristallisation immédiate.

L'ensemble est remis en solution après une ébullition à reflux de 15 minutes. Après refroidissement et filtration on obtient 1,75 g de cristaux, F. 125–128°. Ces cristaux après recristallisation dans le méthanol aqueux fournissent 1,45 g d'ester XVIII, F. 134–136°.
$[\alpha]_D^{22}$ −74,2° ± 1,7°, (0,1337 g dans 20 cm³ d'éthanol absolu).
(Analyse: $C_{21}H_{34}O_3$ (410,6) Calc: C, 78,98; H, 9,33; Tr: C, 78,89; H, 9,5%).

Les eaux-mères de cristallisation qui avaient fourni 1,75 g du produit brut précédent abandonnent, après une nuit de repos au réfrigérateur, le second ester *l*-menthylique XIX. Après filtration et lavage on obtient 1,2 g d'ester, F. 71–73°, qui après recristallisation dans le méthanol fournit 1 g d'ester F. 72–76° (il contient une très petite quantité du premier ester XVIII).
$[\alpha]_D^{22}$ −6,8° ± 1,4° (0,1609 g dans 20 cm³ d'éthanol absolu).
(Analyse: $C_{21}H_{34}O_3$ (410,6) Calc: C, 78,98; H, 9,33; Tr: C, 78,80; H, 9,51%).

Saponification de l'ester l-menthylique XVIII
Obtention du mélange des acides méthyl-2 (méthoxy-6' naphtyl-2')-3 pentanoïques Xg (R = H) *et* XIg (R = H)

3,6 g d'ester *l*-menthylique XVIII sont traités, par 40 cm³ de méthoxy-éthanol et 7,5 cm³ de lessive de soude, à reflux (t°. 125–130°) pendant 15 heures. Après refroidissement on dilue d'eau, extrait à l'éther plusieurs fois et traite la phase sodique par l'acide chlorhydrique; le mélange des acides précipite. Après filtration et lavage à l'eau on en obtient 1,45 g (mélange des acides Xg et XIg).

La phase éthérée précédente est concentrée puis traitée à nouveau 16 heures à reflux (t°. 125–130) par 20 cm³ de méthoxy-éthanol et 3,1 cm³ de lessive de soude. En opérant comme précédemment on obtient de nouveau 0,85 g d'acides (poids total 2,3 g) F. 75–86°.
$[\alpha]_D^{20}$ −16,7° ± 2° (0,9885 g dans 20 cm³ d'éthanol absolu).

Acide diméthyl-2.2 (méthoxy-6' naphtyl-2')-3 pentanoïque XIIg (R = H)

Le mélange des acides Xg et XIg (0,4 g) (obtenu par saponification de l'ester *l*-menthylique XVIII) est traité par le diazométhane. L'ester méthylique est dissous par agitation et sous atmosphère d'azote dans 25 cm³ d'une solution éthérée de triphénylméthyl-sodium (0,135 N).

Après un contact de 45 minutes on introduit, en une seule fois et sous agitation, 2,5 cm³ d'iodure de méthyle. On laisse ainsi plusieurs heures au repos. On lave la phase éthérée à l'eau, sèche sur sulfat de sodium puis chasse le solvant. Le produit brut de la réaction est saponifié par chauffage à l'ébullition pendant 45 minutes avec 5 cm³ de lessive de soude en solution dans 25 cm³ de méthoxy-éthanol. Après refroidissement on reprend par l'eau, épuise à l'éther, précipite la solution sodique par l'acide chlorhydrique dilué. On recueille un acide brut qui après recristallisation du méthanol aqueux donne 200 mg d'acide XIIg (R = H), F. 141–142°.
$[\alpha]_D^{20}$ −23,9° ± 1,3°. (0,167 g dans 10 cm³ d'éthanol absolu).
Ce produit est identique à celui déjà préparé par Horeau et Jacques;[3] le dédoublement est déjà complet.

Méthyl-2 allyl-2 (méthoxy-6' naphtyl-2')-3 pentanoates de méthyle XIIIg (R = CH_3) *et* XIVg (R = CH_3)

(a) *A partir de l'acide* Xg (R = H) *pur.* 1 g d'acide Xg, F. 98–100° $[\alpha]_D$ −22,8° est estérifié par le diazométhane. L'ester méthylique obtenu est dissous sous agitation et sous atmosphère d'azote dans 50 cm³ de triphénylméthyl-sodium (0,145 N). Après un contact de 45 minutes le mélange réactionnel est placé dans la glace, puis traité sous agitation par 6 cm³ de bromure d'allyle fraichement distillé. On abandonne une nuit, on lave la phase éthérée à l'eau, sèche sur sulfate de sodium anhydre, puis élimine l'éther. L'huile brute obtenue est constituée par un mélange des esters des acides recherchés, d'esters initiaux et d'allyl-triphényl-méthane provenant de l'action de l'halogénure d'alcoyle sur le triphénylméthyl-sodium en excès.

1ère-saponification: Afin d'éliminer les esters initiaux plus facilement saponifiables le produit est traité pendant 30 minutes à l'ébullition par 20 cm³ de méthoxy-éthanol et 2 cm³ de lessive de soude 10 N. Après refroidissement on dilue largement d'eau, épuise à l'éther les produits neutres, précipite la solution sodique par l'acide acétique; l'acide qui précipite alors (environ 0,450 g) peut être utilisé comme matière première pour une autre alcoylation.

2éme-saponification: L'extrait éthéré précédent, après évaporation du solvant, est traité pendant 15 heures à l'ébullition par 5 cm³ de lessive de soude et 20 cm³ de méthoxy-éthanol. Après reprise par l'eau, extraction à l'éther, précipitation de la solution sodique par l'acide chlorhydrique on obtient 0,5 g d'un mélange des deux acides diastéréoisomères XIIIg (R = H) et XIVg (R = H). Un échantillon recristallisé dans le méthanol–eau fond à 102–116°.

Cet acide 0,5 g est estérifié par le diazométhane. Les esters obtenus sont introduits en solution dans 4 cm³ d'hexane, sur une colonne d'un diamètre de 2 cm contenant l'alumine (30 g activité IV) et préparée à l'hexane.

Fractions	Volume recueilli (cm³)	Eluant	Substance
1 à 5	5 × 5	Hexane	0
6 à 7	2 × 5	Hexane	0
8	1 × 5	Hexane	Cristaux F. 45–47°
9	1 × 5	Hexane	Cristaux F. 45–47°
10	1 × 5	Hexane	Cristaux F. 45–47°
11	1 × 5	Hexane	Cristaux F. 45–47°
12	1 × 5	Hexane	Huile
13 à 15	3 × 5	Hexane	Huile
16	1 × 10	Hexane	Cristaux impurs
17 à 20	4 × 10	Hexane	Cristaux
21 à 24	4 × 10	Cyclohexane	Cristaux
25 à 27	3 × 10	Cyclohexane C_6H_6 2 : 1	Cristaux F. 53–56°
28 à 30	3 × 10	Cyclohexane C_6H_6 1 : 1	Cristaux
31	1 × 10	Cyclohexane C_6H_6	0

Les fractions 8 à 10 fournissent 0,05 g d'ester méthylique XIIIg (R = CH_3); F. 45–47° que l'on saponifie directement pour obtenir l'acide XIIIg (R = H) F. 151–152° (voir plus loin).

Les fractions 25 à 30 fournissent 0,200 g d'ester méthylique XIVg (R = CH_3) F. 53–55°; acide correspondant XIVg (R = H) F. 53–56°, puis 88–91°.

(b) *A partir du mélange des acides* Xg (R = H) *et* XIg (R = H) *produit de la saponification de l'ester menthylique* XVIII F. 134–136°. 5 g du mélange des acides Xg (R = H) et XIg (R = H), F. 75–86° $[\alpha]_D$ −16,7° sont estérifiés par le diazométhane. Les esters méthyliques obtenus, 250 cm³ de triphénylméthyl-sodium (0,145 mol.) et 10 cm³ de bromure d'allyle sont mis en réaction en observant le mode opératoire précédemment décrit. On lave à l'eau la solution éthérée, sèche sur SO_4Na_2,

et élimine le solvant. L'huile brute est saponifiée en deux étapes. La première saponification est effectuée ainsi: l'huile brute est chauffée pendant 30 minutes à reflux avec 10 cm³ de lessive de soude concentrée et 100 cm³ de méthoxy-éthanol. Après extraction à l'éther et acidification de la phase alcaline on obtient 1,85 g de produit constitué principalement par un mélange d'acides non alcoylés. La deuxième saponification est effectuée ainsi: l'extrait éthéré précédent est chauffé 20 h. à reflux avec 25 cm³ de lessive de soude concentrée et 100 cm³ de méthoxy-éthanol. Après extraction à l'éther et acidification de la phase alcaline on obtient 3,20 g d'acide brut constitué par un mélange des acides XIIIg (R = H) et XIVg (R = H) $[\alpha]_D^{16}$ $-20{,}1° \pm 0{,}2°$ (3,1746 g en solution dans 50 cm³ d'éthanol absolu).

Le mélange précédent est estérifié par le diazométhane puis soumis à la séparation chromatographique sur alumine. Le mélange des esters (3,1 g) est introduit, en solution dans 10 cm³ d'hexane, sur une colonne d'alumine (90g activité IV) préparée à l'hexane

Fractions	Volume (cm³)	Eluant	Substance
1 à 4	4 × 10	Hexane	0
5	10	Hexane	Cristaux F. 45–47°
6	10	Hexane	Cristaux F. 45–47°
7	10	Hexane	Cristaux F. 45–47°
8	10	Hexane	Huile
9 à 17	9 × 20	Hexane	Huile
18 à 20	3 × 20	Hexane	Huile
21 à 28	8 × 20	Cyclohexane	Huile
29	20	Cyclohexane-benzène 1 : 1	Huile
30	20	Cyclohexane	Cristaux
31 à 32	3 × 20	Cyclohexane	Cristaux
33 à 35	3 × 20	Cyclohexane	Cristaux F. 54–55°
36	3 × 20	Cyclohexane	0

Les fractions 5 et 6 fournissent 0,120 g d'ester XIIIg (R = CH_3), F. 45–47° qui conduiront par saponification à l'acide XIIIg (R = H).

Les fractions 7 à 20 soumises à une seconde chromatographie fournissent à nouveau de l'ester F. 45–47°.

Acide méthyl-2 allyl-2 (méthoxy-6' naphtyl-2')-3 pentanoïque XIIIg (R = H)

0,260 mg d'ester F. 45–47°, 12 cm³ de méthoxy-éthanol, 2 cm³ de lessive de soude sont chauffés à reflux pendant 3 heures (t°. 125–130°). On reprend par l'eau, par l'acide chlorhydrique et obtient 0,250 g d'acide coloré. Cet acide est décoloré sur noir dans le méthanol à ébullition, puis recristallisé dans le méthanol aqueux. On obtient 0,137 g d'acide XIIIg (R = H), F. 150–152°. $[\alpha]_D^{20}$ $-55{,}2° \pm 2{,}5°$ (0,0833 g dans 10 cm³ éthanol absolu).
(Analyse: $C_{20}H_{24}O_3$ (312,4) Calc: C, 76,89; H, 7,74; Tr: C, 76,88; H, 7,90%).

Méthyl-2 allyl-2 (méthoxy-6' naphtyl-2')-3 pentanoate de méthyle XIVg (R = CH_3)

Les fractions 33 à 35 fournissent après cristallisation dans le méthanol aqueux 0,130 g d'ester F. 54–55° $[\alpha]_D^{15}$ $-3{,}1° \pm 1{,}5$. (0,128 g dans 20 cm³ éthanol absolu).
(Analyse: $C_{21}H_{26}O_3$ (326,4) Calc: C, 77,3; H, 8,0; Tr: C, 77,0; H, 8,03%).
Les fractions 31 à 32 fournissent 0,900 g d'ester impur. $[\alpha]_D$ $-9{,}75° \pm 2°$; chromatographiées à nouveau elles donnent une nouvelle quantité d'ester XIVg (R = CH_3) pur.

Acide méthyl-2 allyl-2 (méthoxy-6' naphtyl-2')-3 pentanoïque XIVg (R = H)

0,207 g d'ester XIVg (R = CH_3), F. 54–55°; 12 cm³ de méthoxy-éthanol et 2 cm³ de soude concentrée sont chauffés à reflux pendant 3 heures à 125°. Après refroidissement on reprend par l'eau, traite par l'acide chlorhydrique et recueille 0,200 g d'acide. Le produit brut obtenu est décoloré

dans le méthanol à ébullition en présence de noir, puis recristallisé dans le méthanol aqueux. On obtient 0,140 g d'acide XIVg (R = H), F. 53–56°, puis F. 92°. $[\alpha]_D^{20}$ −1,5° ± 1,1° (0,129 g en solution dans 20 cm³ d'éthanol absolu).
(Analyse après séchage plusieurs jours à 40°, F. 90–91°. $C_{20}H_{24}O_3$ (312,4) Calc: C, 76,89; H, 7,74; Tr: C, 76,86; H, 7,95%).

Méthyl-2 allyl-2 (méthoxy-6' naphtyl-2')-3 pentanoates de méthyle XIIId (R = CH_3) *et* XIVd (R = CH_3)

1,950 g d'acide Xd (R = H), F. 98–100° $[\alpha]_D$ +23,5° sont estérifiés par le diazométhane. L'ester méthylique obtenu, 110 cm³ d'une solution 0,145 N de triphénylméthyl-sodium et 4,5 cm³ de bromure d'allyle, sont mis en réaction en observant le mode opératoire déjà décrit plusieurs fois. Après réaction on lave à l'eau la solution éthérée, on la sèche et on élimine le solvant. L'huile brute est saponifiée en deux étapes. La première saponification, par 3 cm³ de lessive de soude et 30 cm³ de méthoxy-éthanol pendant 30 minutes à reflux, permet de récupérer 0,45 g de produit constitué par un mélange d'acides non alcoylés.

La deuxième saponification, effectuée par 1 cm³ de lessive de soude et 40 cm³ de méthoxy-éthanol pendant 12 heures, conduit à 1,3 g d'acide brut, constitué par un mélange d'acides allylés $[\alpha]_D^{20}$ +18,5° ± 0,7 (1,2823 g dans 25 cm³ éthanol absolu).

Le produit brut est estérifié par le diazométhane puis soumis à la séparation chromatographique.

Le mélange d'ester (1,3 g) est introduit en solution dans 13 cm³ d'hexane sur une colonne d'alumine (80 g activité IV) préparée à l'hexane.

On prélève des fractions de 15 cm³ d'éluant.

Fractions	Volume (cm³)	Eluant	Substances
1 à 2	2 × 50	Hexane	0
3	1 × 15	Hexane	0
4 à 8	4 × 15	Hexane	Cristaux F. 45–48°
9 à 11	3 × 15	Hexane	Cristaux F. 45–48°
12 à 14	2 × 15	Hexane	Huile
15 à 23	9 × 15	Hexane	Huile
24 à 31	8 × 15	Hexane-cyclohexane 1 : 1	Huile
32 à 34	3 × 15	Cyclohexane	Huile + cristaux
35 à 39	5 × 15	Cyclohexane–benzène 1 : 1	Cristaux F. 52–54°
40 à 43	4 × 15	Benzène	0

Acide méthyl-2 allyl-2 (méthoxy-6' naphtyl-2')-3 pentanoïque XIIId (R = H)

Les onze premières fractions F. 43–48° sont rassemblées F. 43–48° $[\alpha]_D^{20}$ +56° (0,148 g dans 20 cm³ d'éthanol absolu). La totalité de l'ester soit 0,200 g; 12 cm³ de méthoxy-éthanol, 2 cm³ de soude concentrée sont chauffés 3 heures à reflux à 125°. Après refroidissement on reprend par l'eau, traite par HCl et recueille l'acide brut. Après recristallisation du méthanol aqueux on obtient 0,120 g d'acide XIIId (R = H), F. 152°. $[\alpha]_D^{19}$ +55,2° (0,0779 dans 10 cm³ d'éthanol absolu).
(Analyse: $C_{20}H_{24}O_3$ (312,4) Calc: C, 76,89; H, 7,74; Tr: C, 76,70; H, 7,93%).

Acide méthyl-2 allyl-2 (méthoxy-6' naphtyl-2')-3 pentanoïque XIVd (R = H)

Les fractions 35 à 39 fournissent 0,545 g d'ester que l'on recristallise dans l'éther de pétrole léger on obtient 0,390 g d'ester XIVd (R = CH_3) F. 53–54°.
(Analyse: $C_{21}H_{26}O_3$ (326,4) Calc: C, 77,27; H, 8,03; Tr: C, 77,12; H, 8,08%).

L'ester précédent (0,300 g) est saponifié par chauffage à reflux à 125–130° pendant 3 heures avec 0,8 cm³ de lessive de soude en solution dans 5 cm³ de méthoxy-éthanol. En opérant comme précédemment on obtient 0,200 g d'acide XIVd (R = H), F. 50–53°, puis 92–93°. $[\alpha]_D^{20}$ +1,70° ± 1,2 (0,1647 g dans 5 cm³ d'éthanol absolu). Après séchage plusieurs jours à 40°, F. 93.
(Analyse: $C_{20}H_{24}O_3$ (312,4) Calc: C, 76,90; H, 7,70; Tr: C, 77,10; H, 7,80%).

VOL. 7 1959

Acide méthyl-3 carbométhoxy-3 (méthoxy-6' naphtyl-2')-4 hexanoique XVg

L'ester XIVg, F. 50–54° (0,550 g) en solution dans un mélange de 15 cm³ d'acétone distillée sur permanganate de potassium et 3 cm³ d'eau est traité à 0° et sous agitation par le permanganate de potassium. L'oxydant (0,8 g), finement broyé, est introduit en 5 heures par portions de 0,04 g toutes les 15 minutes. Lors de chaque addition de permanganate on introduit également 0,04 g environ de sulfate de magnésium (SO_4Mg, $7H_2O$).

Le mélange réactionnel est abandonné une journée au réfrigérateur. On essore le précipité qui est constitué en majeure partie par du bioxyde de manganèse et on lave plusieurs fois avec une petite quantité d'acétone.

Le filtrat auquel on ajoute l'acétone de lavage est concentré, repris par l'eau et extrait à l'éther. La phase éthérée est traitée par la potasse à 5%. La phase aqueuse et la solution alcaline de lavage rassemblées sont traitées par l'acide chlorhydrique, elles fournissent un acide impur. (L'extrait éthéré concentré pèse 72 mg.)

Le précipité est mis en suspension dans 80 cm³ d'une solution aqueuse de CO_3K_2 5%, le mélange est porté à 80° puis essoré à chaud. Cette opération est renouvelée plusieurs fois. Les divers filtrats, rassemblés, traités par l'acide chlorhydrique, donnent un acide brut qui est purifié par l'intermédiaire de son di-ester diméthylique suivi d'une saponification sélective.

Cet acide brut (0,460 g) est traité par le diazométhane et le diester méthylique en solution dans 4 cm³ de cyclohexane est passé sur 12 g [d'alumine Merck (activité IV)].

1.	30 cm³ cyclohexane	0
2.	70 cm³ cyclohexane-benzène 8 : 2	0,240 g
3.	60 cm³ cyclohexane-benzène 6 : 4	0,140 g
4.	30 cm³ benzène	0,020 g
5.	60 cm³ alcool méthylique	0,066 g

Saponification sélective

Les fractions 2,3 et 4 de la chromatographie (0,380 g) sont rassemblées, puis traitées à reflux à 90° pendant 6 heures par 8 cm³ d'une solution de 0,566 g de baryte octahydratée dans 16,6 cm³ de méthanol et 11,2 cm³ d'eau. Après refroidissement et repos d'une nuit on traite sous agitation par un mélange d'acide chlorhydrique dilué et d'éther. La solution éthérée est lavée à l'eau, séché sur SO_4Na_2 anhydre. Le solvant est éliminé et le produit brut 0,350 g est recristallisé dans le méthanol aqueux. On obtient 0,212 g d'acide XVd (R = H) les cristaux fondent à 140° quand ils sont posés sur un bloc chauffé lentement; (mais on peut déceler au microscope une première fusion à 59–62° suivie d'une reprise en masse et nouvelle fusion à 140°. Le produit initial solvaté correspond à la formule $C_{20}H_{24}O_5$, $\frac{1}{2}H_2O$.
(Analyse: $C_{20}H_{24}O_5$, $\frac{1}{2}H_2O$ (353,4) Calc: C, 68,0; H, 7,12; Tr. C, 67,70; H, 7,19%).
$[\alpha]_D^{18}$ −3,1° ± 1,5° (0,130 g dans 20 cm³ d'éthanol absolu). Le produit fondant le plus haut correspond à $C_{20}H_{24}O_5$.
(Analyse: $C_{20}H_{24}O_5$ (344,4) Calc: C, 69,75; H, 7,02; Tr: C, 69,73; H, 7,08%).
(après séchage de 30 minutes à 100° F. 140°).

Acide éthyl-1-méthyl-2 oxo-4 méthoxy-7 tétrahydro-1,2,3,4 phénanthrène carboxylique-2 (dextrogyre) XVId (R = H)

L'acide ester XV (R = H) (0,155 g) préalablement privé d'eau de cristallisation par séjour de 30 minutes à 100°, est dissous dans 8 cm³ de benzène déthiophéné anhydre. La solution benzénique est portée dans la glace à 0°. Lorsque le benzène cristallise on introduit en 15 mn et en trois portions 0,180 g de pentachlorure de phosphore, et on laisse en contact à froid pendant 40 mn, en agitant fréquemment.

La masse benzénique jaunit; on ajoute alors dans la solution glacée, en poursuivant l'agitation, 0,4 cm³ de chlorure stannique en solution dans 0,4 cm³ de benzène déthiophéné et on laisse en contact 15 mn à 0°. La masse rouge qui s'est formée est hydrolysée par un mélange de glace et d'acide chlorhydrique en présence d'éther. Après agitation la phase éthérée est décantée, lavée à l'eau, puis reprise avec une solution de potasse à 5%, à nouveau lavée à l'eau et séchée sur sulfate de sodium anhydre. Après élimination du solvant on obtient une huile incristallisable, qui est traitée à reflux

une heure à 125–130° par 0,1 cm³ de lessive de soude et 5 cm³ de méthoxy–éthanol. Après refroidissement, on dilue et acidifie par l'acide chlorhydrique, l'acide précipité est recristallisé, après décoloration sur noir, dans le méthanol aqueux. On obtient 60 mg de céto-acide XVId (R = H) (aiguilles fines) F. 159–160°.

$[\alpha]_D^{19}$ +195° ± 7° (0,0423 g dans 10 cm³ éthanol alcool absolu).

Le spectre infrarouge de ce produit est identique à celui du racémique F. 193° correspondant déjà préparé antérieurement par l'un de nous.[4]

Acide éthyl-1 *méthyl*-2 *méthoxy*-7 *tétrahydro*-1,2,3,4 *phénanthrène carboxylique*-2 XVIId (*acide méthyl*-7(+)*normal bisdéhydrodoisynolique*)

Après avoir vérifié tout d'abord sur le produit racémique correspondant, plus accessible, que les conditions expérimentales suivantes conduisaient bien au produit attendu (déjà obtenu précédemment[4] par réduction du céto-ester, suivi de saponification), nous avons effectué l'essai sur le céto-acide XVId.

On réduit 0,4 g d'oxyde de platine Adams, en suspension dans 5 cm³ d'acétate d'éthyle, par l'hydrogène (10,2 cm³). On introduit 0,2 cm³ d'une solution de chlorure de palladium[11] (0,1 g par cm³) que l'on réduit par l'hydrogène (3,4 cm³ H_2). On introduit alors 0,063 g de céto-acide XVId (R = H), F. 159–160°. Le mélange est agité sous pression et température ordinaire pendant 90 mn; 9,2 cm³ sont ainsi fixés (théorie 7,8 cm³).

Après séparation du catalyseur et élimination du solvant, on obtient 0,060 g d'un produit impur F. 197–209°. Deux recristallisations dans le méthanol aqueux portent le point de fusion à 218°. Litt: 221°.[10] Pouvoir rotatoire du produit (après une seule cristallisation).

$[\alpha]_D^{20}$ +98° ± 13° (0,0148 g dans 10 cm³ d'alcool absolu) Miescher *et al.*[10] donnent +100,5 ± 1,5°.

Mélangé en quantité égale avec un échantillon authentique d'acide (+) méthyl-7 n-bisdéhydrodoisynolique, F. 221° de Rometsch et Miescher,[10] le point de fusion ne subit aucun abaissement: F. 219°. Par contre, mélangé en quantité égale avec un échantillon d'acide (−)méthyl-7 n-bisdéhydrodoisynolique, F. 221°, le point de fusion s'élève à 230° par formation caractéristique du racémique (Miescher *et al.*[10] indiquent F. 228–230°).

[11] E. R. Alexander et A. C. Cope, *Organic Syntheses* **26**, 31 (1946).

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CONTRIBUTION A L'ETUDE DES ALCALOIDES DE L'HOLARRHENA CONGOLENSIS STAPF.

STRUCTURE DE L'HOLARRHENINE

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Résumé—L'identité de l'hydroxy-5α-pregnane, produit de dégradation de l'holarrhénine, avec le 12β-hydroxy-5α-pregnane préparé à partir de la hécogénine confirme la structure de l'holarrhénine comme étant de la 12 β-hydroxyconessine.
Lors de la quaternisation de l'apoholarrhénine en milieu méthanolique, il y a recyclisation avec formation du cycle pyrrolidinique primitif de l'holarrhénine.

Abstract—Degradation of holarrhenin by the Hofmann and Emde reactions results in an hydroxy-5α-pregnane identical with the 12β-hydroxy-5α-pregnane prepared from hecogenin; this definitely establishes the structure of holarrhenin as 12β-hydroxyconessin. The quaternization of apoholarrhenin by methyl iodide in methanol results in cyclization with reestablishment of the primitive pyrrolidin system of holarrhenin.

L'HOLARRHÉNINE, alcaloïde oxygéné signalé pour la première fois en 1919 par Pyman,[1] semble se rencontrer exclusivement dans les espèces africaines du genre Holarrhéna. Depuis le travail de cet auteur, l'espèce africaine, Holarrhéna Congolensis Stapf., n'avait plus fait l'objet de recherches quand, en 1953, Hans et Martin[2] en reprirent l'étude. De l'écorce de cette espèce, ces derniers auteurs ont isolé la conessine, alcaloïde principal, ainsi que l'holarrhénine déjà signalée par Pyman. Le but de cet article est d'établir la structure de ce dernier alcaloïde dont Hans et Martin nous ont obligeamment procuré un échantillon.

Depuis les travaux remarquables de Haworth[3] sur la conessine, l'alcaloïde principal de tous les Holarrhéna, la structure de ce produit est bien connue (V) et elle a été confirmée tout récemment par la synthèse[4] de la dihydroconessine (IV). Ainsi, on établissait en même temps la structure de plusieurs autres alcaloïdes de cette plante pour lesquels S. et R. Siddiqui avaient proposé des structures relatives à celle, inconnue à l'époque, de la conessine.[5] Haworth[3d] a confirmé l'exactitude des hypothèses de Siddiqui et Siddiqui. Dans tous ces alcaloïdes ainsi que dans d'autres (isolés surtout des Holarrhéna de provenance indienne) dont la constitution

[1] F. L. Pyman, *J. Chem. Soc.* 163 (1919).
[2] M. Hans et Fr. Martin, *J. Pharm. de Belg.* 1 (1954).
[3a] R. D. Haworth, J. McKenna et N. Singh, *J. Chem. Soc.* 831 (1949); [b] R. D. Haworth, J. McKenna, et G. H. Whitfield, *J. Chem. Soc.* 3127 (1949); [c] R. D. Haworth, J. McKenna, R. G. Powell et P. Woodward, *J. Chem. Soc.* 1736 (1951); [d] R. D. Haworth, J. McKenna, et G. H. Whitfield, *J. Chem. Soc.* 1102 (1953); [e] R. D. Haworth, J. McKenna, R. G. Powell, et G. H. Whitfield, *J. Chem. Soc.* 1115 (1953).
[4] E. Corey, et W. Hertler, *J. Amer. Chem. Soc.* **80**, 2903 (1958); cfr aussi P. Buchschlacher, J. Kalvodi, D. Arigoni et O. Jeger, *J. Amer. Chem. Soc.* **80**, 2905 (1958).
[5] S. Siddiqui et R. H. Siddiqui, *J. Ind. Chem. Soc.* **11**, 787 (1934).

VOL. 7 1959

a été établie récemment,[6,7] on retrouve un squelette hydrocarboné du type pregna-5-ène avec un atome d'azote lié au carbone 3 et un deuxième attaché au carbone 18 ou 20.

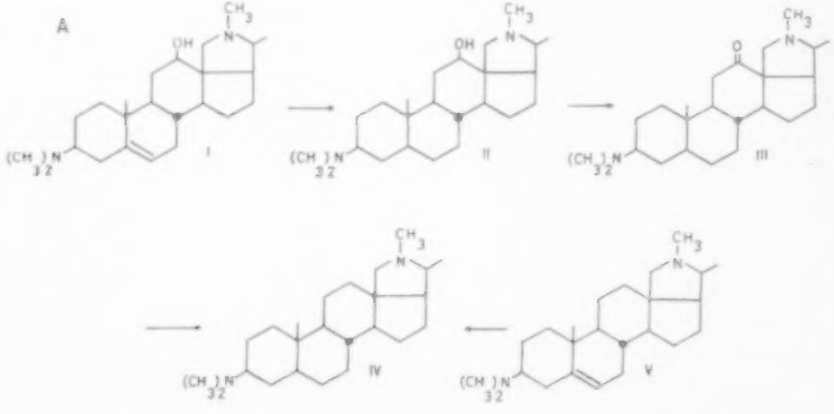
Sur l'holarrhénine elle-même, Pyman nous a laissé les indications suivantes: c'est une substance bibasique de formule brute $C_{24}H_{38}N_2O$ contenant trois liaisons N-alcoyle (très vraisemblablement N—CH_3) et donnant par acétylation un dérivé monoacétylé bibasique, ce qui permet d'envisager la présence d'une fonction hydroxyle.

Nous avons constaté que l'holarrhénine en solution aqueuse acide décolore instantanément le permanganate de potassium à froid; l'hydrogénation catalytique dans l'acide acétique en présence de platine dans les conditions ordinaires de température et de pression est rapide et indique la présence d'une double liaison facilement hydrogénable. La dihydroholarrhénine ainsi obtenue ne décolore plus le permanganate dans les conditions utilisées plus haut.

La quaternisation de la base primitive par l'iodure de méthyle se fait avec fixation de deux molécules d'halogénure et formation d'un sel d'ammonium biquaternaire. En se référant aux données de Pyman (signalées plus haut), ceci permet d'envisager la présence de deux fonctions d'amines tertiaires réparties en une fonction $N(CH_3)_2$ et une fonction NCH_3 faisant partie d'un hétérocycle comme dans la conessine.

Nos analyses de l'holarrhénine et de la dihydroholarrhénine correspondent respectivement à $C_{24}H_{40}N_2O$ et $C_{24}H_{42}N_2O$ (la conessine étant $C_{24}H_{40}N_2$). Pyman avait trouvé un pourcentage trop faible d'hydrogène et admettait la formule brute $C_{24}H_{38}N_2O$ pour l'holarrhénine.

De ce qui précède, il apparaît que l'holarrhénine pourrait être une hydroxyconessine: pour vérifier cette possibilité, il suffisait d'effectuer le passage de la présumée hydroxyconessine à la conessine elle-même en remplaçant la fonction hydroxyle par un atome d'hydrogène. Nous envisagions d'abord cette transformation par réduction du dérivé bromé de l'holarrhénine, malheureusement la préparation de



[6a] R. Tschesche, et A. C. Roy, *Ber.* **89**, 1288 (1956); [b] R. Tschesche et K. Wiensz, *Ber.* **91**, 1504 (1958).
[7a] V. Černý et F. Šorm, *Coll. Czech. Chem. Comm.* **20**, 1473 (1955); [b] L. Labler, V. Černý et F. Šorm, *Coll. Czech. Chem. Comm.* **20**, 1484 (1955); [c] V. Černý, L. Labler et F. Šorm, *Coll. Czech. Chem. Comm.* **22**, 76 (1957); [d] L. Labler et V. Černý, *Chem. Listy* **51**, 2344 (1957); *Chem. Abstr.* **52**, 8165e (1958); [e] V. Černý, L. Labler et F. Šorm, *Chem. Listy* **51**, 2351 (1957); *Chem. Abstr.* **52**, 8166d (1958).

ce dernier par l'action du tribromure de phosphore sur l'holarrhénine donnait lieu à un produit non bromé que nous n'avons pas eu l'occasion d'étudier de plus près (constatations analogues sur d'autres 12-hydroxystéroïdes[8]).

Nous avons alors essayé l'oxydation de la fonction hydroxyle en groupe carbonyle suivie d'une réduction de Huang-Minlon;[9] voir schéma A. Pour éviter des complications lors de l'oxydation à l'aide l'anhydride chromique en milieu acétique, nous avons effectué l'oxydation sur la dihydroholarrhénine (II). Dans la série des stéroides simples, ces oxydations effectuées à l'aide de d'anhydride chromique dans l'acide acétique contenant un peu d'eau se font à la température ambiante, elles sont rapides et donnent de bons rendements en cétones.[10] L'utilisation de ces conditions expérimentales pour la dihydroholarrhénine donne lieu à une réaction lente et incomplète (peut-être à cause de la proximité de l'azote); ce n'est qu'en ajoutant de l'acide sulfurique au milieu réactionnel que la réaction se déroule de façon satisfaisante et fournit une cétone qui donne facilement une oxime. La réduction de cette cétone (III) suivant le procédé de Huang-Minlon donne la désoxy-dihydroholarrhénine identique à un échantillon de dihydroconessine (IV) préparé par hydrogénation catalytique de la conessine (V). La cétone (III) est donc une oxodihydroconessine et la dihydroholarrhénine est une hydroxy-dihydroconessine. Il nous restait encore à localiser la double liaison et la fonction alcool de l'holarrhénine. La position très probable de la double liaison en 5–6 ressort des arguments suivants: 1°. La contribution à la rotation moléculaire de la double liaison de l'holarrhénine est de −181°, valeur qui correspond parfaitement à celles signalées par Haworth[3e] pour une série de produits analogues possédant une double liaison en 5–6 (conessine −169°, 3β-diméthylamino-pregna-5-ène −185°, tétraméthylholarrhimine −167°, conessiméthine −194°) et exclut pratiquement toute autre liaison nucléaire;[11] 2°. Le spectre I.R. présente trois bandes caractéristiques d'une double liaison trisubstituée à 800, 830 et 1656 cm^{-1}.[12] Haworth[3d] indique les valeurs suivantes pour la conessine et pour le 3β-diméthylaminocholest-5-ène respectivement: 798, 826, 1665 et 796, 827, 1660 cm^{-1}. Les positions où la fonction hydroxyle peut se trouver sont fortement limitées si on tient compte des arguments suivants: l'oxodihydroconessine (III) présente dans son spectre I.R. une forte bande carbonyle à 1704 cm^{-1} et une bande α-méthylène à 1422 cm^{-1}: ceci caractérise cette cétone comme hexacyclique et montre qu'elle ne se trouve pas en position 4. La position 11 est exclue car la cétone subit la réduction de Huang-Minlon dans les conditions normales[13] et l'holarrhénine se laisse acétyler dans des conditions douces (exclut 11β). Les seules positions probables pour la fonction hydroxyle se limitent donc à 1, 2, 7 et 12. C'est à ce moment que nous avons eu connaissance du travail d'Uffer[14] sur l'holarrhénine. Dans cet article, l'auteur accumule une série d'arguments très pertinents qui lui permettent d'assigner, par exclusion, la position 12β à la fonction alcoolique de l'holarrhénine (I).

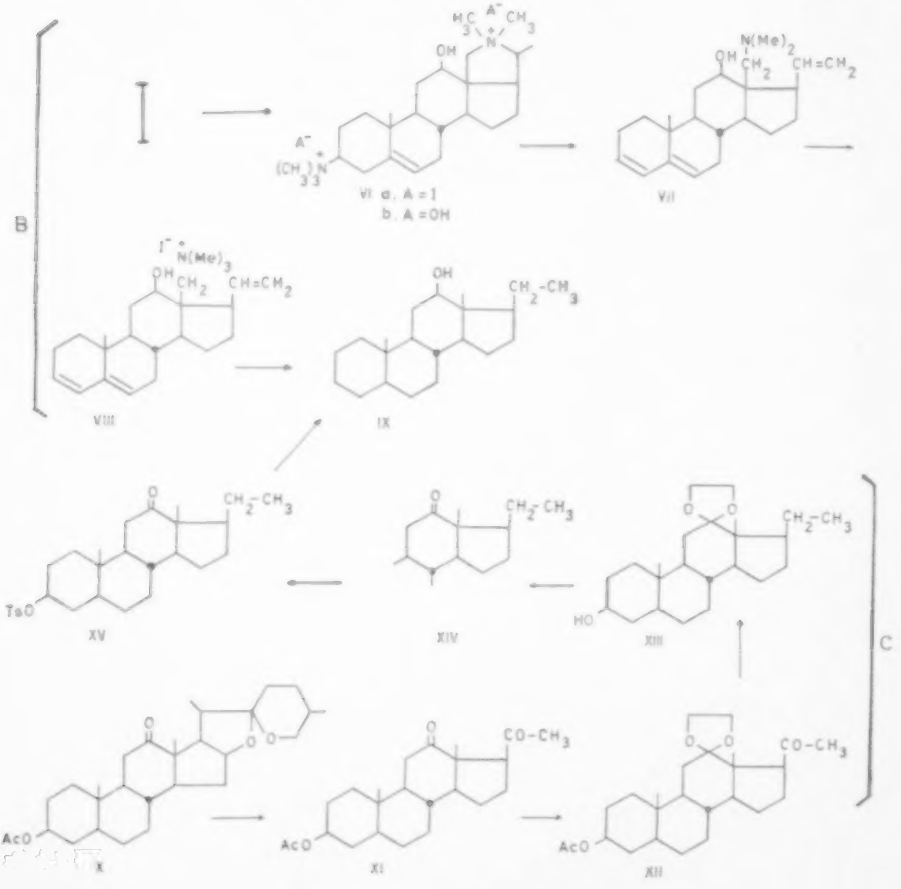
Dès lors, avec l'accord d'Uffer, nous nous sommes efforcés de vérifier de

[8] G. P. Mueller, L. Norton, R. Slobaugh, L. Tsai et R. Winniford, *J. Amer. Chem. Soc.* **75**, 4892 (1953); C. Djerassi, H. Ringold et G. Rosenkranz, *J. Amer. Chem. Soc.* **73**, 5513 (1951).
[9] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).
[10] J. Schreiber et A. Eschenmoser, *Helv. Chim. Acta* **38**, 1529 (1955).
[11] D. H. R. Barton et W. Klyne, *Chem. & Ind.* 755 (1948).
[12] P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch et G. W. Wood, *J. Chem. Soc.* 2402 (1951).
[13] Huang-Minlon, *J. Amer. Chem. Soc.* **71**, 3301 (1949).
[14] A. Uffer, *Helv. Chim. Acta* **39**, 1834 (1946).

la façon suivante la conclusion à laquelle il était arrivé: la dégradation de l'holarrhénine d'après le schèma B devrait nous donner un hydroxy-5α-pregnane contenant la fonction hydroxyle dans la même position nucléaire que la base de départ et identique au produit (IX) que nous préparerons à partir de l'acétate d'hécogénine suivant le schéma C.

Dégradation de l'holarrhénine (*schéma* B)

La dégradation d'Hofmann[14] de la base bisquaternaire (VIb) correspondant au dérivé diodométhylé de l'holarrhénine (VIa) conduit à l'apoholarrhénine; ce produit est transformé en sel d'ammonium quaternaire par action de l'iodure de méthyle en tube scellé et sans autre solvant. La réduction d'Emde de ce sel sous l'action du lithium dans l'ammoniac liquide a fourni un mélange de produits basiques et de produits neutres non saturés; nous avons étudié ces derniers seulement. Le mélange de substances neutres, à l'état brut présente un spectre I.R. dans lequel on retrouve une bande à 900 cm^{-1} attribuée à la double liaison méthylénique terminale de l'apoholarrhénine (VII) et deux bandes dans la région 800–850 cm^{-1} provenant de la réduction partielle du système diénique de cette même base. L'hydrogénation



catalytique s'accompagne de l'absorption de deux moles d'hydrogène et fournit un mélange de produits neutres saturés dont nous avons isolé par chromatographie l'hydroxy-5α-pregnane identique à un échantillon de 12β-hydroxy-5α-pregnane (IX) préparé par le méthode suivante.

Préparation du 12 *β-hydroxy-5α-pregnane* (IX) (*schéma* C)

Nous avons obtenu ce produit en partant du 3β-acétoxy-12,20-dioxo-5α-pregnane (XI), lui-même préparé par dégradation de la hécogénine (X) suivant un procédé connu.[15] Dans le 3β-acétoxy-12,20-dioxo-5α-pregnane, on peut bloquer sélectivement[16,17] la fonction carbonyle en C_{12} sous forme d'éthylènedioxycétal (XII). Nous avons soumis ce cétal à la réduction d'Huang-Minlon[13] plutôt qu'à la réaction de Wolff–Kishner utilisée par Callow *et al.*[16] Contrairement à ces derniers auteurs, nous n'avons pas obtenu directement la substance XIV mais probablement le 12-éthylènedioxycétal (XIII) correspondant, étant donné que cette dernière fonction résiste bien aux conditions basiques:[18] l'hydrolyse du produit en milieu acétique nous donne, avec de bons rendements, le 3β-hydroxy-12-oxo-5α-pregnane (XIV).

Pour réduire, dans cette dernière substance, la fonction 12-céto- en groupement hydroxyle et éliminer simultanément la fonction hydroxyle en C_3, nous avons réduit le dérivé tosylé (XV) du 3β-hydroxy-12-oxo-5α-pregnane par l'hydrure de lithium–aluminium.

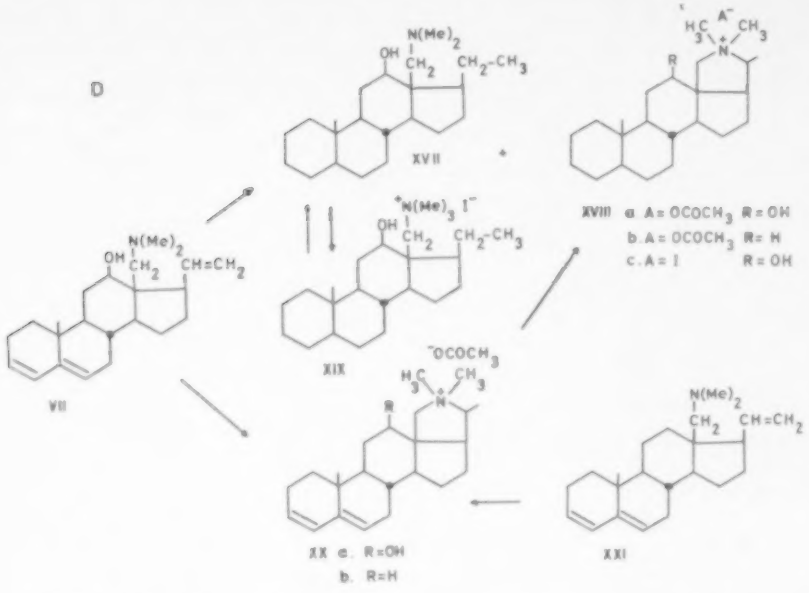
La réduction d'une fonction cétonique en position 12 d'un système stéroïdique par ce réactif n'a pas, à notre connaissance, fait l'objet d'une étude systématique. Si on examine, comme l'a fait Dauben,[19] les deux facteurs qui déterminent la proportion des deux épimères qui peuvent se former dans cette réduction, on constate que l'équilibre thermodynamique favorise la formation de l'épimère 12β et que les conditions stériques favorisent l'attaque du côté α de la molécule[23] soit la formation du même épimère: il nous semble donc que, dans notre réduction, le produit prédominant sera l'épimère 12β.* Du mélange réactionnel obtenu, nous avons, par chromatographie, réussi à isoler un 12-hydroxy-5α-pregnane dont la contribution au pouvoir rotatoire moléculaire de la fonction hydroxyle est 35° (Barton et Klyne[11] signalent 50° pour Δ12β et 93° pour Δ12α;[22]) il s'agit donc très probablement de l'épimère 12β-hydroxy (IX). Ce produit est identique (point de fusion mixte, pouvoir rotatoire spécifique, spectre I.R.) à l'hydroxy-5α-pregnane provenant de la dégradation de l'holarrhénine. (spectres 1 et 2)

L'holarrhénine est donc bien de la 12-hydroxyconessine et probablement l'épimère β; ceci confirme la structure proposée par Uffer (I).

La dégradation de l'holarrhénine, telle que nous l'avons décrite plus haut, a été, en réalité, précédée d'une série d'autres essais partiellement infructueux qui méritent d'être signalés.

* La réduction de l'acétate d'hécogénine par l'hydrure de lithium-aluminium[21] montre que les deux épimères se forment mais qu'il y a prédominance de l'isomère β. Lors de la réduction de la rubijervone[22] par l'hydrure de bore-sodium les auteurs isolent nettement plus de l'épimère 12β que 12α.

[15] A. Cameron, R. Evans, J. Hamlet, J. Hurt, P. Jones et A. Long, *J. Chem. Soc.* 2807 (1955).
[16] R. K. Callow et V. James, *J. Chem. Soc.* 4744 (1956).
[17] W. Adams, D. Kirk, D. Patel, V. Petrow et I. Stuart-Webb, *J. Chem. Soc.* 2298 (1954).
[18] H. J. Dauben, B. Löken et H. Ringold, *J. Amer. Chem. Soc.* **76**, 1359 (1954) note 13.
[19] W. G. Dauben, E. J. Blanz, J. Jiu et Micheli, *J. Amer. Chem. Soc.* **78**, 3752 (1956).
[20] L. F. Fieser, *Experientia* **6**, 313 (1950).
[21] R. Hirschmann, C. Stewart, C. F. Hiskey et N. L. Wendler, *J. Amer. Chem. Soc.* **76**, 4013 (1954).
[22] S. Pelletier et D. Locke, *J. Amer. Chem. Soc.* **79**, 4531 (1957).

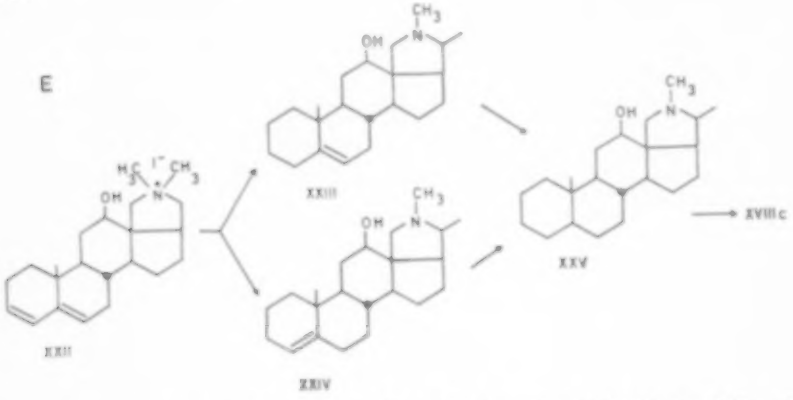


Dans notre schéma primitif (schéma D), nous envisagions la réduction d'Emde, sur l'iodométhylate de l'hexahydroapoholarrhénine. En effet, une réaction analogue effectuée par Haworth[23] sur l'iodure d'ammonium bisquaternaire de la tétrahydroconessiméthine (XVI) avait donné, comme réaction principale, l'élimination de la fonction diméthylamino- en C_{18}. Pour préparer l'hexahydroapoholarrhénine, nous avons soumis l'apoholarrhénine à l'hydrogénation catalytique dans l'acide acétique en présence de platine; nous constatons que l'absorption en hydrogène est déficitaire et se limite à deux et demie molécules environ. Du milieu réactionnel, on isole l'hexahydro-apoholarrhénine (XVII) et un produit secondaire azoté non basique soluble dans l'eau et insoluble dans l'éther; ce produit précipite de la solution aqueuse par addition d'iodure de potassium et doit être le sel quaternaire (XVIIIc) formé par recyclisation de la double liaison méthylénique avec la fonction diméthylamino- en C_{18} et réduction du système diénique. Une telle cyclisation (formation de XXb) est signalée par Haworth[3c] dans le cas de l'apoconessine (XXI) où elle est complète par simple ébullition dans l'acide acétique. Appliqué directement à l'apoholarrhénine (VII), ce traitement nous permet d'isoler un iodure d'ammonium quaternaire (XXa par analogie avec l'apoconessine) dont le spectre I.R. montre la disparition de la double liaison terminale (—CH=CH_2) à 900 cm^{-1} et la subsistance des doubles liaisons conjugées en 3–5. D'autres exemples de formation analogue du cycle pyrrolidine sont signalés par Haworth.[24] L'hydrogénation catalytique de l'acétate correspondant (XXa) dans l'acide acétique en présence de platine entraîne l'absorption de deux molécules d'hydrogène; le sel quaternaire résultant (XVIIIa) isolé sous forme d'iodure (XVIIIc) est identique (spectre I.R., preuve du point de fusion mixte) au produit secondaire isolé lors de l'hydrogénation de l'apoholarrhénine.

[23] R. D. Haworth, L. Lunts et J. McKenna, *J. Chem. Soc.* 3749 (1956).
[24] B. Barley, R. D. Haworth et J. McKenna, *J. Chem. Soc.* 967 (1954).

La quaternisation de l'hexahydroapoholarrhénine (X) par l'iodure de méthyle est beaucoup plus lente que pour les bases dont le cycle pyrrolidinique est intact (holarrhénine, conessine) et s'accompagne, comme le montrent les modèles, d'une forte augmentation d'encombrement stérique. Le sel quaternaire ainsi obtenu (XIX) est soumis à une dégradation modifiée d'Emde[23] par le lithium dans l'ammoniac liquide. Il ne se forme pratiquement pas de produit neutre et on récupère la base initiale (XVII).

La réduction d'Emde classique (à l'amalgame de sodium) appliquée au chlorométhylate de l'apoconessine (XXI.CH_3Cl) donne de bons rendements en produit neutre, tandis que la même reaction appliquée au sel correspondant de l'hexahydroapoconessine donne presque exlusivement la base de départ.[30] Il était donc utile de soumettre à la dégradation d'Emde (Schéma E) le sel quaternaire que nous avions préparé par action de l'iodure de méthyle sur l'apoholarrhénine dans le méthanol (et dont la structure réelle n'est pas VIII mais bien XII, comme nous le montrerons plus loin). La réduction de ce sel par le lithium dans l'ammoniac liquide nous donne très peu de produit neutre exempt d'azote, mais surtout un mélange de bases non saturées.



Le spectre I.R. du produit neutre (dans le domaine 800–850 cm^{-1} il présente une bande importante et unique à 808 cm^{-1}) et l'analyse centésimale nous font supposer qu'il s'agit d'un 12-hydroxy-5α-pregnane-4-ène. Par recristallisation fractionnée, on sépare difficilement et incomplètement le mélange des bases en deux constituants: le premier fond vers 160°, présente une rotation spécifique $(\alpha)_D^{21} = 114°$ et possède dans son spectre I.R. une bande à 808 cm^{-1} (Δ4) et deux petites bandes à 798 et 832 cm^{-1} à attribuer à une impureté ayant une double liaison en 5–6; le deuxième fond vers 228° présente $(\alpha)_D^{21} = 10°$ et présente dans son spectre I.R. deux fortes bandes à 798 et 833 cm^{-1} dues à une double liaison en 5–6. Lors de l'hydrogénation catalytique dans l'acide acétique en présence de platine, les deux produits absorbent chacun une mole d'hydrogène en donnant naissance à une base saturée unique fondant à 216,6–217,4° (avec un rendement nettement plus élevé à partir de la base non saturée en 5–6 qu'à partir de l'autre); les deux bases de départ sont donc des isomères différant par la position d'une double liaison. Ce produit d'hydrogénation est différent de l'hexahydroapoholarrhénine (F 161–162°), son spectre I.R. présente dans la région de 1000–1050 cm^{-1} une seule bande très importante (à 1040

VOL.
7
1959

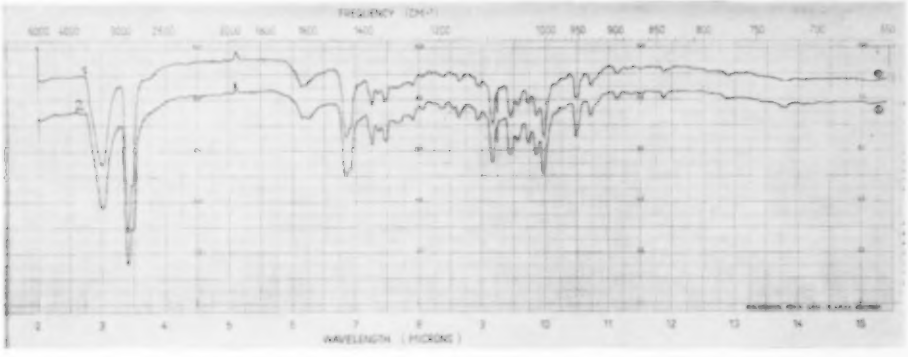


FIG. I.

cm^{-1}) caractéristique qu'on retrouve pour les dérivés de l'holarrhénine dans lesquels le cycle pyrrolidinique subsiste (quand le cycle est ouvert nous constatons la présence de plusieurs bandes d'égale intensité). En tenant compte de la structure du produit de départ (VII), cette dernière constatation, ainsi que l'analyse du nouveau produit, nous conduit à envisager XXV comme structure de cette substance. Remarquons que, dans ce cas, son sel quaternaire (iodométhylate) correspondant doit être identique à XVIIIc préparé plus haut (schéma D): effectivement la quaternisation de XXV par l'iodure de méthyle est très rapide (contrairement aux bases dont le cycle pyrrolidinique est ouvert) et donne lieu à un sel quaternaire identique (fusion mixte, spectre I.R.) à XVIIIc: ceci confirme la structure XXV et conduit aux structures XXIV (F 160°) et XXIII (F 228°) pour les deux précurseurs de cette base.

Devant ce résultat inattendu de la dégradation d'Emde, nous avons eu des soupçons en ce qui concerne l'identité de l'iodure quaternaire de départ (soi-disant VIII); il s'agissait de savoir si le cycle pyrrolidinique se reformait pendant la réaction d'Emde ou au cours de la quaternisation de l'apoholarrhénine (VII). Dans la dernière éventualité, le sel quaternaire obtenu doit être identique à l'iodure de XXa préparé plus haut: la comparaison des spectres I.R. et l'épreuve de point de fusion mixte montrent qu'il en est bien ainsi. Le peu de produit neutre isolé provient donc probablement d'un peu de sel quaternaire normal (VIII) formé secondairement.

Il est curieux de constater que les auteurs qui ont effectué la dégradation d'Emde sur l'apoconessine VIIIb[25,3a] ne semblent pas observer de cyclisation lors de la quaternisation préalable de la base; or, ces auteurs préparent le sel quaternaire par simple chauffage du produit en tube scellé avec de l'iodure de méthyle sans autre solvant.

Dans notre expérience, le méthanol, utilisé comme solvant, a donc favorisé la cyclisation de l'apoholarrhénine; en n'utilisant lors de la quaternisation que l'iodure de méthyle lui-même comme solvant, la quaternisation -comme le montre la première partie du travail a lieu normalement (schéma B). On peut rapprocher de notre expérience celle réalisée par Haworth qui cyclise l'apoconessine par chauffage pendant 4 heures et à 150°, en présence d'alcool aqueux à 90°.

PARTIE EXPERIMENTALE

Remarques

1° Les points de fusion sont corrigés et ont été pris en capillaire et sous vide.
2° Le pouvoir rotatoire est déterminé en solution chloroformique sur des solutions dont la concentration est de l'ordre de 1%.
3° Les spectres I.R. ont été pris avec du produit dispersé dans le bromure de potassium à des concentrations de l'ordre de 0,5%.

Holarrhénine (I) isolement:[2,14] Purifié par recristallisation dans l'acétate d'éthyle. F 198,5–199°

$C_{24}H_{40}N_2O$ (372,58)	calc.	C 77,36	H 10,82%
	trouvé	C 77,23	H 10,85%

O-*Acétylholarrhénine*: On dissout 200 mg d'holarrhénine dans un mélange de 1 cc de pyridine anhydre et 1 cc d'anhydride acétique puis on laisse reposer la nuit. On verse le tout dans l'eau glacée, on basifie à la soude et on extrait le précipité blanc à l'éther. La solution éthérée est lavée à l'eau jusqu'à neutralité. L'évaporation sous vide de cette solution, séchée sur sulfate de magnésium

[25] E. Späth et O. Hromatka, *Ber.* 63, 126 (1930).

anhydre donne le dérivé acétylé qui est purifié par recristallisation dans l'acétone. F 177,8–178,4°

$C_{26}H_{42}N_2O_2$ (414,61)	calc.	C 75,3	H 10,2	N 6,8%
	trouvé	C 75,4	H 10,5	N 6,9%

Di-iodométhylate d'holarrhénine: Dans un mélange de 10 cc de méthanol et 3 cc d'iodure de méthyle fraîchement distillé, on dissout 1,51 g d'holarrhénine; on chauffe à reflux pendant 2 heures. On maintient le milieu réactionnel en ébullition, on y ajoute 5 cc d'acétone et ensuite, goutte à goutte, de l'éther anhydre jusqu'à fin de précipitation: le sel quaternaire, légèrement jaune, cristallise. On filtre les cristaux et on les lave à l'ether absolu: 2,6 g F 310° déc (bain 295°).* On recristallise le sel dans un mélange d'éther, acétone et méthanol.

$C_{24}H_{46}N_2OI_2$ (632,46):	calc.	C 47,6	H 7,1%
	trouvé	C 47,9	H 7,2%

Dihydro-holarrhénine (II): On soumet à l'hydrogénation une solution de 300 mg d'holarrhénine dans 10 cc d'acide acétique pur pour analyse en présence de 27 mg de platine d'Adams (à 20°, pression ordinaire). Après une heure, la réduction est pratiquement arrêtée. Après 5 heures, (absorption d'une mole d'hydrogène) on filtre la suspension et on lave le platine plusieurs fois avec un peu d'acide acétique. Les solutions acides sont concentrées sous vide à température ordinaire (jusqu'à environ 4 cc). On verse la solution acétique dans une solution de soude à 5% et on extrait le précipité blanc à l'éther: on lave l'extrait éthéré à l'eau et on le sèche sur sulfate de magnésium. La solution éthérée évaporée à sec donne 280 mg de produit brut F 178–181°. Ce produit est relativement peu soluble dans l'acétone dont il recristallise en longues aiguilles. On le purifie par recristallisation dans l'acétone, puis dans l'acétate d'éthyle (où il est nettement plus soluble). F 185,5–186°. $[\alpha]_D^{28}$ +44,5° ± 3 (C = 1,73).

$C_{24}H_{42}N_2O$ (374,59)	calc.	C 76,94	H 11,30	N 7,48%
	trouvé	C 77,25	H 11,40	N 7,43%

O-*acétyldihydroholarrhénine*: cf. préparation de l'acétylholarrhénine décrite plus haut. Recristallisé dans un mélange d'eau-acétone, il fond à 141–141,5°

$C_{28}H_{44}N_2O_2$ (416,63)	calc.	C 74,9	H 10,6%
	trouvé	C 74,6	H 10,5%

Di-iodométhylate de dihydroholarrhénine: On dissout à froid 40 mg de dihydroholarrhénine dans un mélange de 1 cc de chloroforme sec et de 0,5 cc d'iodure de méthyle: après quelques minutes la solution se trouble. Le lendemain, un liquide gélatineux s'est déposé au fond du récipient; en triturant ce produit avec un peu d'éther anhydre, il se solidifie. On décante le liquide surnageant et on recristallise le sel quaternaire dans un mélange d'acétone-méthanol auquel on ajoute progressivement de l'éther anhydre (au fur et à mesure de la cristallisation): 62 mg. F 315° déc (bain 305°). Après recristallisation: 315,7–316,2° déc.

$C_{26}H_{44}N_2OI_2$ (658,5)	calc.	C 47,4	H 7,4%	
	trouvé	C 47,3	H 7,6%	

12-*Oxodihydroconessine* (III): A 300 mg de dihydroholarrhénine dissous dans 15 cc d'acide acétique pur pour analyse, contenant 0,6 cc d'acide sulfurique aqueux (1/1 en volume), on ajoute, en agitant, 150 mg d'anhydride chromique dissous dans un mélange de 3 cc d'acide acétique et de 3 cc d'eau. On maintient, durant toute l'addition (15'), la température en dessous de 25°. Au début, il se forme un précipité verdâtre qui se dissout progressivement par la suite. Après l'addition d'acide chromique on maintient le mélange réactionnel pendant 30' encore à température ordinaire, puis on détruit l'excès d'acide chromique par addition de 10 ml de méthanol (30'). La solution verte est ramenée à environ 5 ml sous vide; on y ajoute de l'eau et de la glace, puis on basifie à l'aide de soude à 10%, jusqu'à dissolution des sels de chrome. On extrait la suspension à l'éther. La solution éthérée lavée jusqu'à neutralité, est séchée sur sulfate de magnésium puis évaporée à sec: 250 mg

* Le chiffre entre parenthèses indique la température du bain au moment où le capillaire est introduit dans l'appareil à point de fusion.

F 188–190°. On recristallise le produit brut dans de l'éther de pétrole 60–80°: aiguilles blanches F 191–191,8°

$C_{24}H_{40}N_2O$ (372,58)	calc.	C 77,4	H 10,8%
	trouvé	C 77,2	H 11,1%

$[\alpha]_D^{20} = +80° \pm 2°$ (C = 0,96).

Oxime de la 12-*oxo-dihydroconessine*: On mélange 110 mg de la cétone à 350 mg de chlorhydrate d'hydroxylamine et 10 ml de méthanol. On dissout le tout à l'ébullition puis on laisse reposer pendant 24 heures; on verse le tout dans de l'eau glacée et on alcalinise. Le précipité blanc est filtré et lavé à l'eau. On le recristallise dans le méthanol: petits cristaux incolores F 260.6–261,2°.

$C_{24}H_{41}N_3O$ (387,59)	calc.	C 74,3	H 10,7%
	trouvé	C 73,8	H 10,5%

VOL. 7 1959

Apoholarrhénine (VII): Le diodométhylate d'holarrhénine préparé plus haut est transformé en base d'ammonium quaternaire par passage de sa solution à 15% dans un mélange éthanol-eau (5/1) sur échangeur d'ions (I.R.A. 400 chargé d'OH^-).[26] Pour la suite des opérations cfr Uffer.[14] On recristallise le produit réactionnel dans l'éthanol: F 156,4–157,2°. $[\alpha]_D^{20}$ $-86° \pm 4°$. [A. Uffer: $[\alpha]_D^{20}$ $-87° \pm 4°$].

Dihydroconessine (IV) *par réduction de la* 12-*oxodihydroconessine* (III): A un mélange de 0,5 ml d'hydrazine pure et de 0,5 g de soude caustique pulvérisé dans 5 ml de diéthylèneglycol, on ajoute 50 mg du dérivé cétonique. On chauffe pendant 1 heure au bain d'huile à 120°, puis on amène progressivement la température à 215–220° pendant qu'on distille l'eau formée et l'hydrazine en excès: on maintient cette température pendant 3 heures. Au mélange réactionnel, on ajoute de l'eau et on extrait la base organique à l'éther: on sèche la solution éthérée (sulfate de magnésium), puis on évapore à sec: 39 mg d'huile qui se solidifie par addition d'un peu d'éther de pétrole: F 98–103°: chromatographie sur papier de ce produit parallèlement à de la dihydroconessine préparée par hydrogénation de la conessine, donne une tache unique dont le R_f est identique à celui de la dihydroconessine.

On recristallise le produit brut dans l'acétone: F 107–107,8° point de fusion mixte avec de la dihydroconessine (F105 — 106,5°) : 105 — 106, 5°

Hexahydroapoholarrhénine (XVII): On soumet à l'hydrogénation 200 mg d'apoholarrhénine dans 5 cc d'acide acétique en présence de 16 mg de platine d'Adams (20°, pression ordinaire). Après environ 30', l'absorption s'arrête: ceci correspond à environ 2,4 moles d'hydrogène. De la façon habituelle, on isole la base: 106 mg recristallisé dans l'acétone, fond à 160–161°. La solution aqueuse (après extraction de la base) est extraite au chloroforme. La solution chloroformique est filtrée et évaporée à sec. Le solide jaune est repris par le minimum d'eau; on y ajoute une solution d'iodure de potassium (10%) dans l'eau et on essore le précipité légèrement jaune de l'iodure quaternaire XVIIIc qui, séché, fond à 263–265°.

$C_{23}H_{41}NO$ (347,57)	calc.	C 79,5	H 11,9%
(Hexahydroapoholarrhénine)	trouvé	C 80,0	H 11,9%

$[\alpha]_D^{21}$ $+33°$ ($c = 0{,}947$) M_D $+115°$

Le dérivé *acétylé* (préparé comme 1'O-acétylholarrhénine) est purifié par recristallisation: F 106–106,4°.

I.R. 1738, 1238 cm^{-1}.

Iodométhylate de l'hexahydroapoholarrhénine (XIX): On fait refluer pendant 20 heures une solution de 260 mg d'hexahydroapolholarrhénine dans 6 cc d'un mélange à volumes égaux de méthanol et d'iodure de méthyle. On concentre fortement (jusqu'à environ 2 ml) le milieu réactionnel et on ajoute, goutte à goutte, de l'éther anhydre à la solution: il cristallise environ 275 mg de petits cristaux F 258–260° déc. Les eaux-mères éthérées sont concentrées et recyclées dans une opération analogue: on isole encore 48 mg de cristaux F 257° déc.

[26] J. Weinstock et V. Boekelheide, *J. Amer. Chem. Soc.* **75**, 2546 (1953).

Cyclisation de l'apoholarrhénine par l'acide acétique: Aprés avoir chauffé à reflux 50 mg d'apoholarrhénine dans 10 ml d'acide acétique pendant 30', on concentre la solution à environ 1/2 à 1 ml. L'addition et la basification par la soude ne produisent aucun précipité dans ce mélange. A la solution aqueuse, on ajoute une solution aqueuse d'iodure de potassium: un précipité blanc se forme immédiatement, on le filtre, on le lave à l'eau et on le sèche: 55 mg F 261–268° déc. On dissout le produit dans de l'acétone contenant un minimum de méthanol et, à la solution chaude, on ajoute progressivement de l'éther anhydre: le produit cristallise en petites aiguilles blanches: F 275–277° déc. (XXa mais I^- au lieu de $OCOCH_3^-$). Le spectre I.R. ne présente plus la bande $CH{=}CH_2$ à 900 cm^{-1} de l'apoholarrhénine, dans la région de 1000–1050 cm^{-1} il ne reste plus qu'une bande forte à 1040 cm^{-1}.

Iodométhylate de la desdiméthylamino-dihydroholarrhénine (XVIIIc): On fait refluer 100 mg d'apoholarrhénine dans 5 cc d'acide acétique pour analyse. Après 30', on refroidit la solution et on y ajoute 9,2 mg de platine d'Adams. On hydrogène ce milieu réactionnel à 20° (pression ordinaire): après environ 30', deux moles équivalents d'hydrogène ont été absorbés et la réaction s'arrête pratiquement. Après une heure, on arrête l'hydrogénation, on filtre le catalyseur et on basifie le filtrat: à la solution aqueuse, on ajoute une solution d'iodure de potassium. Il se produit un abondant précipité blanc qu'on filtre, lave et sèche: 130 mg F 258° env. Ce produit est recristallisé dans un mélange d'acétone-éther et donne de petits cristaux incolores F 268–270°: pas d'abaisement de point de fusion avec le produit secondaire isolé lors de l'hydrogénation de l'apoholarrhénine: avec le produit non hydrogéné (voir préparation précédente), il y a abaissement. Ce produit-ci est d'ailleurs beaucoup plus soluble dans l'acétone que le sel quaternaire non saturé.

$C_{23}H_{40}NOI$ (473,48)	calc.	C 58,3	H 8,5%
	trouvé	C 58,4	H 8,3%

Spectre I.R. absence de la bande méthylénique $-CH{=}CH_2$ à 900 cm^{-1}; plus de non-saturation dans la région 800–850 cm^{-1}.

Réduction d'Emde de l'iodométhylate de hexahydroapoholarrhénine (XIX): On ajoute, en une fois, 286 mg du sel quaternaire (XIX) à 200 cc d'ammoniac liquide distillé et sec auquel, tout en agitant, on a ajouté du lithium jusqu'à persistance de la coloration bleue. On maintient la coloration par addition de lithium. Après avoir agité pendant 8 heures, on laisse s'évaporer l'ammoniac. La poudre blanche qui reste est additionnée d'eau; on acidifie la suspension et on extrait la fraction neutre a l'éther. Après lavage de l'extrait éthéré à l'acide chlorhydrique dilué, on lave à l'eau jusqu'à neutralité; on sèche la solution éthérée (sulfate de magnésium), puis on l'évapore à sec On isole ainsi 5 mg d'un produit fort impur que nous n'avons pas examiné plus loin.

Après l'extraction de la fraction neutre, on basifie la solution aqueuse à l'aide d'une solution de soude caustique et on extrait le produit basique à l'éther: après traitement de la solution éthérée comme d'habitude, on en isole environ 190 mg de base qu'on recristallise dans l'acétone: 145 mg F 161–162° identique à l'hexahydroapoholarrhénine (XVII).

Quaternisation de l'apoholarrhénine (VII) *à l'aide d'iodure de méthyle dans le méthanol*: On dissout 1,4 g d'apoholarrhénine dans 16 cc d'un mélange à volumes égaux d'iodure de méthyle et de methanol. On fait refluer cette solution pendant 24 heures. On distille 9 a 10 cc de solvant puis on ajoute, à l'ébullition, goutte à goutte, de l'éther anhydre jusqu'à trouble persistant, puis, dès que des cristaux se séparent, on continue l'addition jusqu'à fin de précipitation. Le lendemain, on filtre le solide et on le lave à l'éther anhydre: 1,49 g de petits cristaux blancs F 273° déc. (bain 250°). Les eaux-mères contiennent encore de l'apoholarrhénine; on recycle la base comme on vient de le décrire. De cette manière, on isole encore 310 mg de cristaux F 273–273° (dans les eaux-mères, on retrouve encore environ 80 mg d'apoholarrhénine impure (F 150–155°). Après recristallisation dans un mélange d'acétone-alcool méthylique (auquel on ajoute de l'éther anhydre), le sel quaternaire fond à 278–279° déc. Ce produit s'est montré identique à celui résultant de la cyclisation de l'apoholarrhénine dans l'acide acétique (voir plus haut) (XXa iodure correspondant).

Réduction d'Emde du sel quaternaire précédent: On effectue cette réduction comme décrit plus haut; on y a engagé 850 mg de sel quaternaire, et on a ajouté 0,5 ml de méthanol à l'ammoniac liquide. On isole une fraction neutre (23 mg brut) et environ 500 mg de bases brutes.

Par recristallisation du produit neutre dans l'acétone, on isole une substance qui fond à 166–166,5°. Spectre I.R. bande importante à 807 cm^{-1}: double liaison en 4–5? (pas de bande à 900 cm^{-1})

$C_{21}H_{34}O$ (302,48)	calc.	C 83,4	H 11,3%
	trouvé	C 83,2	H 11,2%

Par recristallisation de la fraction basique dans l'alcool méthylique suivie de cristallisation fractionnée dans l'acétone, on sépare deux produits: le moins soluble cristallise en petites aiguilles fines, fond à 226–230° et présente $(\alpha)_D^{22}$ +10° tandis que l'autre cristallise en petits cristaux trapus qui fondent à 156–158° $(\alpha)_D^{21}$ +116°. Les spectres I. R. de ces deux produits indiquent pour le premier une double liaison en 5–6 (798, 833 cm^{-1}) et pour le deuxième en 4–5 (808 cm^{-1}).

Malheureusement, les analyses de ces produits ne sont pas très satisfaisantes et leurs structures probables (XXIII et XXIV) découlent plutôt de leurs produits d'hydrogénation.

$C_{22}H_{35}NO$ (329,51)	calc.	C 80,2	H 10,7%
F 226–230°	trouvé	C 79,4	H 10,7%
F 156–158°		C 78,9	H 10,9%

Hydrogénation de la base F 226–230°: On soumet à l'hydrogénation catalytique 39,6 mg de base dans 2 ml d'acide acétique pour analyse contenant 5,3 mg de platine d'Adams (à 20° et pression ordinaire). Après 16', la réduction est terminée (1 mole H_2 absorbé) et on arrête la réduction après 3 heures. De la manière habituelle, on isole 38 mg de produit brut F 200–210°. Ce produit est recristallisé dans l'acétone et donne un échantillon analytique fondant à 216,6–217,4°; $[\alpha]_D^{20}$ + 49,5° (XXV)

$C_{22}H_{37}NO$ (331,52)	calc.	C 79,7	H 11,25%
	trouvé	C 79,4	H 11,3%

Le spectre I.R. de ce produit ne présente plus les bandes de non-saturation du produit de départ.

Hydrogénation de la base F 156–158°: 60 mg de base sont hydrogénées dans des conditions analogues à celles de l'hydrogénation précédente. On absorbe 1 mole d'hydrogène en 11 minutes, puis la réaction s'arrête: on isole 31 mg de petites aiguilles blanches F 214–216° identiques au produit isolé dans l'hydrogénation précédente.

Quaternisation de la base hydrogénée F 216–217° (XXV): On dissout 24 mg de base dans 0,5 ml d'iodure de méthyle en tube scellé et on met le tube au bain-marie: après une minute, un produit solide se sépare. Après 12 heures, on ouvre le tube, on évapore à sec et on met le résidu en suspension dans de l'éther anhydre. Par filtration, on isole environ 38 mg de produit brut F 258–262°. On recristallise ce produit de la manière habituelle dans un mélange de méthanol, acétone, éther: petits cristaux incolores F 265–267° (Fusion mixte avec l'iodométhylate de desdiméthylaminodihydroholarrhénine (XVIIIc): 266–268°, Spectres I.R. identiques).

Quaternisation de l'apoholarrhénine par l'iodure de méthyle sans solvant: On dissout 185 mg d'apoholarrhénine dans 1,5 ml d'iodure de méthyle fraîchement distillé et on chauffe la solution en tube scellé pendant 40 heures à 85–95°. Par refroidissement, le sel quaternaire cristallise en oursins. On décante l'excès d'iodure de méthyle, on sèche les cristaux au bain-marie, puis on les lave à l'éther anhydre: 225 mg F 198–205°. Ce produit brut est utilisé tel quel dans la réduction d'Emde qui suit. Son spectre I.R. indique la même non-saturation que dans l'apoholarrhénine.

Réduction d'Emde de l'iodométhylate d'apoholarrhénine (VIII): On réduit 1,12 g de sel quaternaire comme décrit pour l'iodométhylate d'hexahydroapoholarrhénine. En tout, on a ajouté environ 160 mg de lithium. Le résidu blanc (après évaporation de l'ammoniac) est décomposé à l'eau; on extrait la suspension à l'éther, il reste environ 180 mg de produit brun pâle, non dissous, que nous n'avons pas examiné plus loin. De la solution éthérée, on extrait les bases à l'aide d'une solution d'acide chlorhydrique 2 N (de ces solutions acides, on extrait 190 mg de bases non examinées) puis on la lave à l'eau, à la soude diluée et enfin à l'eau jusqu'à neutralité: la solution séchée (sulfate de magnésium) et évaporée donne 300 mg d'un solide pâteux exempt d'azote. Ce produit est encore fortement non-saturé.

VOL. 7 1959

Hydrogénation catalytique du produit neutre de la réaction précédente: L'hydrogénation est réalisée dans des conditions analogues à celles déjà décrites plus haut (ex. dihydroholarrhénine): elle s'arrête après l'absorption de 2,2 moles d'hydrogène; on isole du milieu réactionnel 286 mg de produit brut pâteux; la recristallisation dans un mélange acétone-eau, suivie de recristallisation dans un mélange méthanol-éther, donne 110 mg de produit blanc à point de fusion très peu net autour de 140°. On chromatographie ce produit sur 4 g d'alumine neutre Woelm activité I dans l'éther de pétrole. L'élution à l'aide d'éther de pétrole ne donne pratiquement pas de produit. A l'aide d'un mélange progressivement plus riche d'éther dans l'éther de pétrole, on isole environ 55 mg de produit blanc solide fondant entre 145–148°; le reste de produit, isolé en ajoutant des quantités croissantes d'éthanol à l'éther pur, donne des produits huileux. On recristallise le solide F 145–148° dans l'acétone: aiguilles blanches très fines F 152–152,6°

Les eaux-mères provenant de la recristallisation du produit brut de l'hydrogénation sont évaporées à sec et le résidu chromatographié sur 10 g d'alumine dans des conditions analogues à la première chromatographie: on n'a pas réussi à isoler de produit bien défini de ces fractions.

3-*Hydroxy*-5α-*pregnan*-12-*one* (XIV): On introduit 870 mg de 3β-acétoxy-12,12-éthylènedioxy-5α-pregnane dans un mélange de 10 ml de diéthylène glycol, 4 ml d'hydrazine anhydre et 1 g de potasse caustique pulvérisée. Après avoir chauffé une heure à reflux au bain d'huile, on élève la température progressivement à 230° (température du bain), tout en distillant l'excès d'hydrazine et l'eau formée. On maintient cette température pendant environ 4 heures, on refroidit la solution, on y ajoute de l'eau et on extrait le milieu réactionnel à l'éther. La solution éthérée bien lavée à l'eau est séchée et évaporée à sec: 735 mg de cristaux blancs F 161–163°. On dissout ce produit dans 10 cc d'acide acétique à 90% et on chauffe pendant 1 heure au bain-marie. La solution est diluée à l'eau, on neutralise par de la soude à 10% en présence de glace et on extrait la suspension à l'éther. La solution éthérée, séchée et évaporée, abandonne 650 mg de solide blanc F 185–189°. On le recristallise dans l'acétone F 194,5–196,5° $[\alpha]_D^{21}$ +107° (lit:[16] $[\alpha]_D^{20}$ +109°).

3β-*Tosyloxy*-5α-*pregnan*-12-*one* (XV): On dissout 300 mg de 3β-hydroxy-12-oxo-5α-pregnane dans 4 ml de pyridine anhydre; on y ajoute, en refroidissant dans le glace, une solution de 360 mg de chlorure de paratoluènesulfonyle dans 2 cc de pyridine anhydre. Après 16 heures à 6°, on verse le tout sur de la glace pilée, on ajoute de l'eau et on extrait le dérivé tosylé à l'éther. L'évaporation à sec de la solution éthérée, lavée et séchée, donne 420 mg de produit blanc F 132–138°. Par recristallisation dans le méthanol, seul ou contenant un peu d'acétate d'éthyle, on obtient de petites aiguilles F 146,5–147°.

$C_{35}H_{50}SO_4$ (472,66)	calc.	C 71,1	H 8,5	S 6,8%
	trouvé	C 71,0	H 8,5	S 6,7%

12-*Hydroxy*-5α-*pregnane* (IX): On extrait 360 mg du dérivé tosylé précédent se trouvant dans un creuset filtrant au-dessus d'une suspension de 200 mg d'hydrure de lithiumaluminium dans 25 ml d'éther anhydre, en faisant refluer l'éther tout en agitant mécaniquement. On fait refluer pendant 4 heures, puis on abandonne la réaction pendant 10 heures. On décompose le milieu réactionnel avec de l'eau tout en agitant et on dissout le précipité d'hydroxyde d'aluminium par addition d'acide chlorhydrique à 10%. La couche éthérée est décantée et on y ajoute l'extrait éthéré de la solution aqueuse. La solution éthérée est lavée successivement à la soude 0,5 M et à l'eau, séchée et évaporée à sec: 227 mg solide blanc F 108–127°. On chromatographie ce produit sur 10 g d'Alumine neutre Woelm act. II dans l'éther de pétrole (on porte le produit sur la colonne dans un mélange de 1 cc benzène et de 2 cc éther de pétrole). On commence l'élution par l'éther de pétrole 40–60 (fractions de 10 cc). Les 13 premières fractions donnent environ 40 mg de produit qui par recristallisation dans l'acétone fondent entre 120–128°. Les fractions suivantes (jusqu'à 40) ainsi que les fractions obtenues par élution à l'aide d'éther de pétrole contenant des proportions croissantes (jusqu'à 50%) de benzène, donnent 120 mg de produit blanc solide fondant sur un large intervalle de température et qui, par recristallisation dans l'acétone, donnent environ 50 mg fondant vers 150°. On continue l'élution par le benzène pur, auquel on ajoute des quantités croissantes d'éther anhydre: pratiquement plus rien ne s'élue. On ajoute alors un mélange d'éther anhydre-chlorure de méthylène contenant des quantités croissantes de chlorure de méthylène. Avec le chlorure de méthylène pur, on isole

encore 45 mg de produit F 159–164° (probablement un mélange de 3β-,12(α ou β)dihydroxy-5α pregnanes.

Le produit fondant vers 150° est purifié par recristallisation dans l'acétone, suivie d'une sublimation sous 10^{-2} mm à la température de 110° (température du bain): F 153,6–154,2°. Il n'y a pas d'abaissement de point de fusion avec le produit résultant de la dégradation d'Emde de l'iodométhylate d'apoholarrhénine, suivie d'hydrogénation; spectre I.R. identique.

$[\alpha]_D^{20}$ +25,6° (c = 1,19) M_D 78° ± 5°

$C_{21}H_{36}O$ (304,5)	calc.	C 82,8	H 11,9%
	trouvé	C 82,6	H 11,8%

Les eaux-mères des recristallisations de produits des fractions éluées à l'éther de pétrole et l'éther de pétrole-benzène ont été rechromatographiées sur de l'alumine Woelm neutre d'activité. I. L'élution avec l'éther de pétrole et le benzène ne donne rien. En présence d'éther, l'élution commence et, par recristallisation des résidus dans l'acétone, on isole encore du produit à point de fusion 151–152, identique au produit isolé plus haut.

VOL. 7 1959

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Que Monsieur A. Uffer veuille bien trouver ici l'expression de notre gratitude pour l'intérêt constant et amical qu'il a porté à notre travail et pour les intéressantes discussions que nous avons eues ensemble.

Les analyses et les spectres I.R. ont été faits respectivement par Madame S. Franck et Monsieur G. van Binst dans le service de Monsieur le Professeur R. H. Martin, nous les en remercions bien since-rement.

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SYNTHESIS OF SOME ISOQUINOLINE DERIVATIVES*

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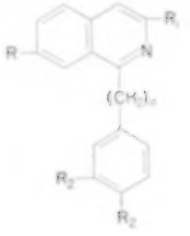
Abstract—The Bischler–Napieralski reaction has been applied to the synthesis of several isoquinoline derivatives related to papaverine but devoid of one or two methoxyl groups in positions 6 and 7.

THE isoquinoline derivatives Ia, b, c, d related to papaverine have been synthesized[1] with the object of subsequently investigating their physiological properties and to determine the influence of methoxyl groups in positions 6 and/or 7.



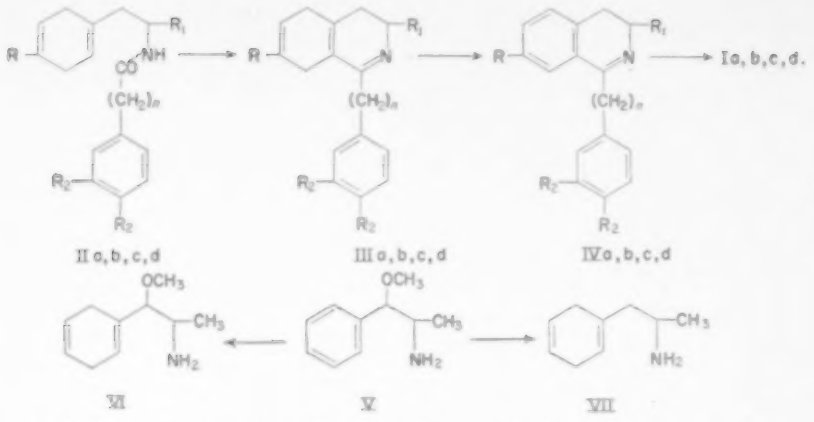
Ia,b,c,d

a: $R = R_2 = H$, $R_1 = OCH_3$, $n = 1$
b: $R = H$, $R_1 = CH_3$, $R_2—R_3 = O—CH_2—O$, $n = 1$
c: $R = H$, $R_1 = CH_3$, $R_2—R_3 = O—CH_2—O$, $n = 0$
d: $R = OCH_3$, $R_1 = H$, $R_2 = OCH_3$, $n = 1$

Ia was synthesized by condensing β-cylcohexa-1,4-dienylethylamine with 3,4-dimethoxyphenylacetyl chloride giving IIa which was cyclized forming the unstable intermediate IIIa. The latter on dehydrogenation gave IVa which was also obtained by cyclizing N-(3′,4′-dimethoxyphenylacetyl)-β-phenylethylamine. Further dehydrogenation of IVa by palladium in boiling ethyl cinnamate gave 1-(3′,4′-dimethoxybenzyl)-isoquinoline Ia. The structure of Ia is supported by the results of analyses and U.V. spectrum giving by Noller *et al.*[2] for papaverine.

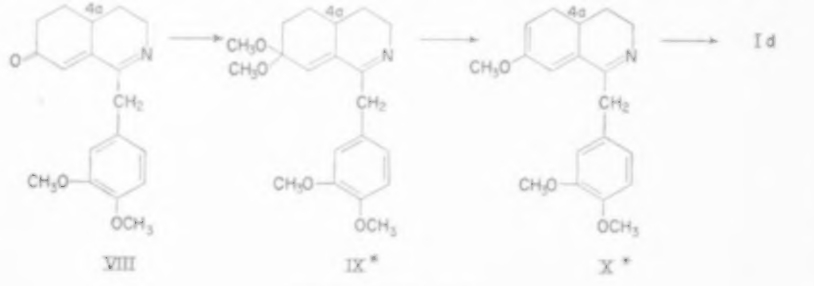
Ib and Ic were synthesized by condensing 3-(cyclohexa-1′,4′-dienyl)-1′-(2-aminopropane) VII with 3,4-methylenedioxyphenylacetyl and 3,4-methylenedioxybenzoyl chlorides respectively, the products in each case being cyclized and dehydrogenated giving Ib and Ic. The amine VII was prepared by reducing 3-phenyl-3-methoxy-2 aminopropane V according to Birch,[3] and during the reaction the methoxyl group is removed. VI was therefore not obtained. VII was also prepared from propenyl-

[1] S. Sugasawa and R. Tachikawa, *Tetrahedron* In press.
[2] R. C. Noller and R. Azima, *J. Amer. Chem. Soc.* **72**, 18 (1950).
[3] A. J. Birch, *J. Chem. Soc.* 430 (1944); cf. also A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.* **75**, 5360 (1953).



benzene which was converted to 1-methoxy-1-phenyl-nitropropane via the nitrosite, and on reduction with lithium aluminium hydride gave V which by Birch's method gave VII.

For the synthesis of Id 4-methoxyphenylethylamine is reduced[1] to β-4-methoxycyclohexa-1,4-dienylethylamine, and the crude base was condensed with 3,4-dimethoxyphenylacetyl chloride yielding N-(3,4-dimethoxyphenylacetyl)-β-cyclohexa-1,4-dienylethylamine IId. Cyclization of the latter with phosphoryl chloride gave a poor yield[4] of the base IIId mixed with unchanged IId and resinous matter. Dehydrogenation of the mixture of IId and IIId gave the dihydro base IVd which was further dehydrogenated to Id. An alternative route for the synthesis of Id started from the crude base (obtained by cyclizing IId) which was treated with acid, yielding the keto-base VIII in which the presence of the conjugated keto group was indicated by the I.R. spectrum (1668 cm^{-1}). VIII was converted to the dimethylketal IX containing four methoxyl groups. Treatment of IX with aluminium t-butoxide[5] yielded with loss of one methoxyl group the unstable base X which was dehydrogenated giving Id.



EXPERIMENTAL

N-(3',4'-Dimethoxyphenylacetyl)-β-cyclohexa-1,4-dienylethylamine (IIa)

β-Cyclohexa-1,4-dienylethylamine (6·2 g) in benzene (80 cc) during stirring and cooling was treated dropwise with freshly distilled 3,4-dimethoxyphenylacetyl chloride dissolved in 100 cc benzene

* III. Communication of Extension of Bischler–Napieralksi Reaction by S. Sugasawa. II. Communication S. Sugasawa and S. Ushioda, *Tetrahedron* In press.

† The positions of the double bonds in these compounds are not exactly located.

[4] N. Itoh and S. Sugasawa, *Tetrahedron* **1**, 45 (1957).

[5] S. M. McElvain and G. R. McKay, *J. Amer. Chem. Soc.* **77**, 5601 (1955).

in the presence of 200 cc 5% $NaHCO_3$ solution. After the addition of about 80% of the chloride the amide separated and was kept in solution by addition of ethyl acetate. After stirring a further 2 hr at room temp the supernatant layer yielded the amide (13·8 g; 91·6%) which crystallized from benzene: n-hexane as colourless needles, m.p. 111–112°. (Found: C, 71·5; H, 7·6; N, 4·55. $C_{18}H_{23}O_3N$ requires: C, 71·8; H, 7·6; N, 4·65%).

1-(3′,4′-*Dimethoxybenzyl*)-3,4-*dihydroisoquinoline* (IVa)

(a) The amide (IIa, 2·0 g) in 30 cc benzene mixed with 2 cc phosphoryl chloride was refluxed gently on a steam-bath for ½ hr. The solvent and the excess of phosphoryl chloride were removed *in vacuo* and the residue dissolved in dil HCl. The acid solution was basified and the liberated base taken up in benzene, washed, dried and the solvent removed. The residue (1·8 g), probably IIIa in 30 cc xylene was added to Pd-C (0·4 g of 30%) and the mixture refluxed for 3 hr in an atmosphere of N_2. The Filtrate free from catalyst was evaporated and the residue distilled *in vacuo* yielded a yellow viscous syrup (1·65 g) b.p. 194–197°/0·08 mm, U.V. λ_{max}^{EtOH} 271 mμ (log ε 3·81), 312 mμ (log ε 3·31), 323 mμ (log ε 3·33). This was characterized as a crystalline picrate from ethanol, m.p. 154–155°. (Found: C, 56·0; H, 4·0; N, 10·7; $C_{24}H_{22}O_9N_4$: requires C, 56·5; H, 4·3; N, 11·0%).

(b) N-(3′,4′-Dimethoxyphenylacetyl)-β-phenylethylamine (6·0 g) m.p. 113–114° (Found: C, 71·9; H, 6·8; N, 4·9. $C_{18}H_{21}O_3N$ requires: C, 72·2; H, 7·0; N, 4·7%), in 200 cc xylene and phosphorus pentoxide (30 g) added in two portions during 1·5 hr was refluxed for 5 additional hr. The product purified through an alumina column, was a yellow oily substance (0·35 g) which gave a picrate m.p. 155–155·5° identical with that obtained by method (a).

1-(3′,4′-*Dimethoxybenzyl*)*isoquinoline* (Ia)

A solution of the above-mentioned base (2·0 g) in 20 cc ethyl cinnamate was heated over Pd-C (0·2 g, 30%) in an atmosphere of N_2 at 220–230° for 2·5 hr. On cooling the catalyst was filtered, washed with benzene and the combined benzene-filtrate shaken with 10% HCl. The acid solution, was basified and the liberated base, a yellowish brown syrup (1·73 g.) was again dissolved in benzene and purified through an alumina column. The product (1·52 g or 76·2%), crystallized from n-hexane as colourless needles m.p. 71–72°; U.V. λ_{max}^{EtOH} 274 mμ (log ε 3·76), 311 mμ (log ε 3·49), 323 mμ (log ε 3·54). (Found: C, 77·3; H, 5·9; N, 5·0. $C_{18}H_{17}O_2N$ requires: C, 77·4; H, 6·1; N, 5·0%).

The *picrate* was crystallized from ethanol, m.p. 164°. (Found: C, 56·8; H, 4·1; N, 10·8. $C_{24}H_{20}O_9N_4$ requires: C, 56·7; H, 3·9; N, 11·0%).

Propenylbenzene pseudonitrosite

Dilute sulphuric acid (410 g, 20%) was added dropwise with stirring and cooling to a mixture of propenyl benzene (30 g in 250 cc ether) and an aqueous solution of sodium nitrite (120 g). Solid pseudonitrosite separated but stirring was continued for an additional hour and the product then washed successively with water, a small amount of methanol and ether and dried, yield 26·3 g, m.p. 116–118° (decomp). (Found: C, 55·3; H, 5·2; N, 14·35. $(C_9H_{10}O_3N_2)_2$ requires: C, 55·7; H, 5·2; N, 14·4%).

1-*Methoxy*-1-*phenyl*-2-*nitropropane*

The pseudonitrosite (15 g) was added in small portions to a methanolic solution of KOH (100 cc, 10%) in a stoppered bottle and shaken into solution. Glacial acetic acid was added until the solution was neutral, the solvent evaporated *in vacuo* and sufficient water added to dissolve inorganic matter, with separation of an oily substance. The latter in benzene was washed, dried and evaporated to a yellow liquid, which distilled at 112–114°/5 mm, yielding 12·5 g (83·2%).

3-*Phenyl*-3-*methoxy*-2-*aminopropane* (V)

To a cooled ethereal solution of $LiAlH_4$ (6 g) was added dropwise with cooling and stirring an ethereal solution of the foregoing nitro-compound (13·8 g). After treatment with cold water and evaporation of the ethereal solution, the yellow oily base dissolved in dilute HCl was shaken with benzene, and basified with conc NaOH solution. The base in benzene was dried, the solvent evaporated and the residue distilled *in vacuo* in an atmosphere of H_2. The amine (8·8 g, 75·3%) distilled at 93–95°/6 mm. The *hydrochloride* formed colourless needles m.p. 186–188° from ethanol–acetone. (Found: C, 59·45; H, 8·1; N, 7·05; OCH_3, 15·2; $C_9H_{12}N(OCH_3)$ HCl requires: C, 59·55; H, 7·9; N, 6·95; OCH_3, 15·4%).

3-(*Cyclohexa*-1,4-*dienyl*)-1′-(2-*aminopropane*) (VII)

The amine (V, 6·6 g) in absolute ethanol (18·3 g) mixed with 100 cc liquid ammonia was reduced by adding 2·8 g lithium in small portions and cooling in ethanol–dry ice. After addition of the metal the mixture was stirred until the blue colouration disappeared. The crude base was distilled *in vacuo* in an atmosphere of H_2, yielding 5·2 g (95·3%) of a colourless clear distillate b.p. 71–72°/5 mm, which gave a negative result on CH_3O determination.

N-(3,4-*Methylenedioxyphenylacetyl*)-β-*cyclohexa*-1,4-*dienylisopropylamine* (IIb)

This was prepared as usual and formed colourless plates from n-hexane : benzene, m.p. 108–109°. The yield was 91·5%. (Found: C, 72·2; H, 6·8; N, 4·9; $C_{15}H_{21}O_3N$ requires: C, 72·2; H, 7·0; N, 4·7%).

VOL. 7 1959

1-(3,4-*Methylenedioxybenzyl*)-3-*methyl*-3,4-*dihydroxyisoquinoline* (IVb)

This was obtained in a yield of 71·3% by cyclizing IIb followed by dehydrogenation as described. U.V. λ_{max}^{EtOH} 276mμ (log ε 3·80), 318 mμ (log ε 3·46), 326 mμ (log ε 3·44). *Picrate*: Yellow prisms from ethanol, m.p. 170–171° (decomp). (Found: C, 57·0; H, 4·1; N, 10·9; $C_{24}H_{20}O_9N_4$ requires: C, 56·7; H, 3·9; N, 11·0%).

1-(3,4-*Methylenedioxybenzyl*)-3-*methylisoquinoline* (Ib)

This forms colourless prisms m.p. 87–88° from n-hexane; U.V. λ_{max}^{EtOH} 278 mμ (log ε 3·89), 317 mμ (log ε 3·54), 329 mμ (log ε 3·56). The yield was 77·3% from (IVb). (Found: C, 77·7; H, 5·6; N, 5·1; $C_{18}H_{15}O_2N$ requires: C, 78·0; H, 5·4; N, 5·05%). The *picrate* separated in yellow needles from ethanol–glacial acetic acid, m.p. 180°. (Found: C, 57·0; H, 3·9; N, 11·1; $C_{24}H_{18}O_9N_4$ requires: C, 56·9; H, 3·6; N, 11·1%).

N-(3′,4′-*Methylenedioxybenzoyl*-β-*cyclohexa*-1,4-*dienylisopropylamine* (IIc)

This forms colourless needles m.p. 83–84° from n-hexane. (Found: C, 71·6; H, 6·8; N, 5·2; $C_{17}H_{19}O_3N$ requires: C, 71·6; H, 6·7; N, 4·9%).

1-(3,4-*Methylenedioxyphenyl*)-3-*methyl*-3,4-*dihydroisoquinoline* (IVc)

This is obtained as a yellow syrup in 76·4% yield from IIc by cyclization and dehydrogenation. U.V. λ_{max}^{EtOH} 259 mμ (log ε 3·95), 293 mμ (log ε 3·83). The *picrate* forms yellow prisms from ethanol, m.p. 175–176° (decomp). (Found: C, 55·6; H, 3·6; N, 11·3; $C_{23}H_{15}O_9N_4$ requires: C, 55·9; H, 3·6; N, 11·3%).

1-(3′,4′-*Methylenedioxyphenyl*)-3-*methylisoquinoline* (Ic)

This was obtained in 72·5% yield by dehydrogenation of IVc and formed colourless needles m.p. 74–75° from n-hexane. U.V. λ_{max}^{EtOH} 285 mμ (log ε 3·96), 333 mμ (log ε 3·87). (Found: C, 77·3; H, 5·1; N, 5·3; $C_{17}H_{13}O_2N$ requires: C, 77·6; H, 4·9; N, 5·3%). The *picrate* forms yellow needles from ethanol, m.p. 184°. (Found: C, 55·85; H, 3·4; N, 11·4; $C_{23}H_{16}O_9N_4$ requires: C, 56·1; H, 3·25; N, 11·4%).

β-4-*Methoxycyclohexa*-1,4-*dienylethylamine*

4-Methoxyphenethylamine was reduced according to Birch's method and yielded a colourless liquid (92·1%) b.p. 78–78·5°/1 mm after distillation in an atmosphere of H_2. U.V. λ_{max}^{EtOH} 277 mμ (log ε 1·72). This base is fairly unstable and discolourizes gradually.

N-(3,4-*Dimethoxyphenylacetyl*)-β-*cyclohexa*-1,4-*dienylethylamine* (IId)

The foregoing base was treated with 3,4-dimethoxyphenylacetyl chloride to form IId (90·2%) which separated from benzene : n-hexane in colourless needles m.p. 91–93°. (Found: C, 68·6; H, H, 7·9; N, 4·1; $C_{19}H_{23}O_4N$ requires: C, 68·9; H, 7·55; N, 4·2%).

1-(3′,4′-*Dimethoxybenzyl*)-7-*methoxy*-3,4-*dihydroisoquinoline* (IVd)

A mixture of the amide (IId, 2 g) in benzene (50 cc) and phosphoryl chloride (2 cc) was gently refluxed on a steam-bath for 10–15 min. To the cooled mixture sufficient dry petroleum–ether was

added to cause a reddish oil to separate. After standing the supernatant layer was discarded and the base extracted with benzene (ca. 100 cc), and addition of 100 cc 10% NaOH with vigorous shaking. The benzene layer was dried over K_2CO_3, the solvent evaporated *in vacuo* in an atmosphere of N_2 leaving a brown syrup, which in absolute xylene was refluxed over 30% Pd-C (0·5 g) in an atmosphere of N_2 for 4 hr. Filtered free from the catalyst the solvent was removed *in vacuo* and the residue in 10% HCl extracted with benzene, basified with NaOH solution, and the benzene, washed, dried and evaporated *in vacuo*. A brown residue dissolved in a mixture of n-hexane and benzene was filtered through an alumina column yielding a yellow syrup (0·21 g, 11·2%). U.V. λ_{max}^{EtOH} 277 mμ (log ε 3·83), 310 mμ (log ε 3·37), 321 mμ (log ε 3·89). This was characterized as a crystalline *picrate*, m.p. 159–161° (decomp) from acetone. (Found: C, 55·3; H, 4·2; N, 10·0; $C_{23}H_{24}O_{10}N_4$ requires: C, 55·6; H, 4·4; N, 10·4%).

1-(3′,4′-*Dimethoxybenzyl*)-7-*methoxyisoquinoline* (Id)

This was obtained by dehydrogenation of IVd and formed colourless needles m.p. 85–86° from n-hexane, yield 60·4%, U.V. λ_{max}^{EtOH} 277 mμ (log λ 3·85), 313 mμ (log ε 3·61), 323 mμ (log ε 3·63). (Found: C, 74·0; H, 6·3; N, 4·6; OCH_3, 29·85; $C_{19}H_{19}O_3N$ requires: C, 73·8; H, 6·15; N, 4·5; OCH_3, 30·1%). The *picrate* crystallizes in yellow prisms from ethanol : acetic caid, m.p. 171°. (Found: C, 55·45; H, 4·2; N, 10·6; $C_{25}H_{22}O_{10}N_4$ requires: C, 55·8; H, 4·1; N, 10·4%).

1-(3′,4′-*Dimethoxybenzyl*)-7-*oxo*-3,4,4a,5,6,7-*hexahydroisoquinoline* (VIII)

The crude reddish oil, obtained by cyclizing IId with phosphoryl chloride was acidified with 10% HCl and undissolved matter was removed by extraction with benzene. The acid solution with benzene was warmed (steam-bath) for several min, cooled and basified with Na_2CO_3 solution and the benzene, washed, dried and part of the solvent evaporated. The residual solution was filtered through an alumina column and a yellow syrup obtained on evaporation of the solvent. The base (39·8%) solidified and crystallized from n-hexane: acetone in pale yellow prisms m.p. 176–178°. I.R. ν_{max}^{Nujol} 1668 cm^{-1} (>C=C—C=O). (Found: C, 71·9; H, 6·8; N, 4·7; OCH_3, 20·3; $C_{16}H_{21}ON(OCH_3)_2$ requires: C, 72·2; H, 7·0; N, 4·7; OCH_3, 20·7%).

The 2:4-*dinitrophenylhydrazone sulphate* crystallized as red needles m.p. 212–214° (decomp) from ethanol. (Found: C, 49·55; H, 4·8; N, 12·0; $C_{24}H_{28}O_8N_5H_2SO_4$ requires; C, 49·9; H, 4·7; N, 12·1%).

1-(3′,4′-*Dimethoxybenzyl*)-7,7-*dimethoxy*-3,4,4a,5,6,7-*hexahydroisoquinoline* (IX)

To a well cooled mixture of the oxo-compound (VIII, 0·6 g) and methyl orthoformate (4 cc) dry hydrogen chloride was bubbled and the mixture refluxed (steam-bath) for 2·5 hr. Excess formate was distilled off and the dark brown residue well kneaded with powdered K_2CO_3 (2 g), covered with ether and dilute K_2CO_3 solution (20 cc, 5%) added with cooling.

The aqueous layer was extracted with ether and the ethereal solution dried (K_2CO_3) and evaporated. The resultant brown residue in benzene : n-hexane was filtered through an alumina column and 0·32 g (46·2%) of a yellow syrup obtained. (Found: OCH_3, 35·3; $C_{16}H_{15}N(OCH_3)_4$ requires: OCH_3, 35·9%). The methiodide was prepared as usual and formed yellow prisms m.p. 198–201° (decomp) from ethanol. (Found: C, 51·5; H, 5·9; N, 3·1; $C_{21}H_{31}O_4NI$ requires: C, 51·6; H, 6·2; N, 2·9%).

1-(3′,4′-*Dimethoxybenzyl*)-7-*methoxyisoquinoline* (Id)

The ketal (IX, 0·25 g) in a small amount of benzene was well mixed with a few drops of aluminum t-butoxide in benzene and the residue obtained by evaporation of the solvent was heated (oil-bath) at 200–220° in an atmosphere of N_2 for 2 hr. The product was extracted with benzene, mixed with n-hexane, and filtered through an alumina column. On evaporating the filtrate the reddish oil (0·11 g) was dehydrogenated in boiling ethyl cinnamate over Pd-C. The product (0·05 g, 22·3%) m.p. 85–86° was not depressed on admixture with Id obtained by the alternative method.

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VOL. 7 1959

PYROLYTIC ELIMINATION OF ACETATES

ISOTOPE EFFECT, RELATIVE REACTIVITY AND MECHANISM[1]

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(*Received* 13 *March* 1959)

Abstract—By comparing the exo–endo olefin ratio in the pyrolysis of 1-methylcyclohexyl acetate and of 1-methylcyclohexyl acetate-2,2,6,6-d_4, the deuterium isotope effect for the acetate pyrolysis reaction has been determined to be 1·7 at 500° and 1·9 at 400°. These values are to be compared with the theoretical maximum values of 2·1 and 2·3 respectively. By carrying out competitive pyrolyses it has been possible to determine some relative rates of pyrolysis which show that no appreciable positive charge is developed in the transition state of the reaction. It is further shown that the presence of hetero substituents changes the pattern of the pyrolysis in a predictable way, and rules are formulated whereby the products to be expected from a given pyrolysis can be predicted. A convenient synthesis of cyclohexenone is described.

THE pyrolytic elimination of acetates to form olefins has been a very useful synthetic reaction, especially for the preparation of olefins from alcohols which rearrange under acidic dehydration conditions, and for the preparation of terminal olefins from primary acetates. The pyrolytic elimination of unsymmetrical secondary and tertiary acetates has been investigated by Bailey and co-workers[3] and it was claimed that these esters cleanly pyrolyze so as to form exclusively the olefin bearing the least number of alkyl groups (Hofmann rule[4]). It has recently been shown, however, that these results of Bailey were in error, that actually all pyrolytic acetate eliminations lead to mixtures of olefins, and that the most highly substituted olefin actually predominates in cyclic cases.[5–8]

Despite the fact that the more recent work has shown the pyrolysis to be less selective than the earlier reports, we have demonstrated that the products formed from a pyrolytic elimination can be rationalized in terms of statistical, steric and thermodynamic effects,[5] and it is the purpose of the present paper to discuss new experiments which help elucidate the details of the mechanism, and to present rules, firmly based on experimental data, which will enable the relative amounts of products to be expected from a given pyrolysis to be predicted. It is hoped that the acetate pyrolysis will then gain a place among the most common laboratory procedures.

Since the cyclic, *cis* character of the reaction is well recognized,[9] we shall confine

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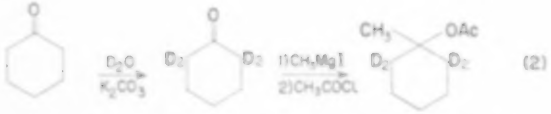
[2] Procter and Gamble summer research fellow, 1957 and 1958.
[3a] W. J. Bailey and C. King, *J. Amer. Chem. Soc.* **77**, 75 (1955); [b] W. J. Bailey, J. J. Hewitt and C. King, *J. Amer. Chem. Soc.* **77**, 357 (1955).
[4] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 427 *et seq.* Cornell University Press, N.Y. (1953).
[5] D. H. Froemsdorf, C. H. Collins, G. S. Hammond and C. H. DePuy, *J. Amer. Chem. Soc.* **81**, 643 (1959).
[6] W. H. Bailey and W. F. Hale, *J. Amer. Chem. Soc.* **81**, 647 (1959).
[7] E. E. Royals, *J. Org. Chem.* **23**, 1822 (1958).
[8] R. A. Benkeser and J. J. Hazdra, *J. Amer. Chem. Soc.* **81**, 228 (1959).
[9] E. R. Alexander and A. Mudrak, *J. Amer. Chem. Soc.* **73**, 59 (1951).

our discussion to a consideration of the two bond-breaking processes, namely the breaking of the C—H and the C—O bonds (equation 1). We will be most interested

(i)

in the timing of these two processes, and in the effect of substituents on the ease of such breaking. We shall then be able to describe the transition state in some detail.

If we examine first the carbon–hydrogen bond-breaking process, we are struck by the fact that for non-cyclic acetates the Hofmann product predominates. However, we have shown[5] that steric and statistical factors favor the formation of the least substituted olefins and that, *other conditions being equal, the ease of hydrogen removal in acetate pyrolyses is that predicted by operation of the Saytzeff rule*, i.e. $3^\circ > 2^\circ > 1^\circ$. If the hydrogen is benzyl, then its removal is favored,[10] but the effect of the phenyl is not to acidify the hydrogen but to stabilize the incipient double bond.[11] Strongly acidifying groups attached to the carbon bearing the hydrogen (e.g. C=O, NO_2) may favor its removal,[10a] but here experimental data are still contradictory.[12] We considered it of interest to examine the deuterium isotope effect in the acetate pyrolysis reaction, because the magnitude of this effect is generally considered to be a measure of the amount of bond-breaking in the transition state.[13] Curtin and Kellom[14] had arrived at a value of $2{\cdot}8 \pm 0{\cdot}6$ for this isotope effect, but because this value was determined only incidentally to another study the error was unavoidably large, and in addition the system in which it was determined (1,2-diphenylethyl acetate) might not be typical for aliphatic acetates. Kinetic experiments at the temperatures required for this reaction are difficult to perform, so we were led to study relative rates by an internal competition method. The synthetic aspects of the reaction are summarized in equation (2).



(2)

We pyrolyzed samples of 1-methylcyclohexyl acetate and its deutero analog (I) under identical conditions and determined the ratio of the olefinic products formed. These results are reported for 400° and 500° in Table 1. Making the reasonable assumption that the rate of pyrolysis into the exocyclic methyl group is the same in both compounds, it is possible to calculate the deuterium isotope effect quite easily. It is seen that by this method relatively large values for k_H/k_D are found, indicating that the carbon–hydrogen bond is being broken in the transition state. On the other hand they are significantly less than the theoretical maxima[15] at these temperatures

[10a] W. J. Bailey and C. King, *J. Org. Chem.* **21**, 858 (1956); [b] C. G. Overberger, E. M. Pearce and D. Tanner, *J. Amer. Chem. Soc.* **80**, 1761 (1958).

[11] C. H. DePuy and R. E. Leary, *J. Amer. Chem. Soc.* **79**, 3705 (1957).

[12] See ref. 10a, footnote 11.

[13] K. B. Wiberg, *Chem. Rev.* **56**, 713 (1956).

[14] D. Y. Curtin and D. B. Kellom, *J. Amer. Chem. Soc.* **75**, 6011 (1953).

[15] If there were no C—H bond-breaking in the transition state then k_H/k_D would be unity. On the other hand if the hydrogen were transferred in the rate determining step, and the reaction were so concerted that the forming O—H bond exactly compensated for the breaking C—H bond, then only the mass differences would be important and k_H/k_D would be $\sqrt{2}$. The experimental value of 1·9 falls half-way between this value and the theoretical maximum for no bonding to hydrogen in the transition state.

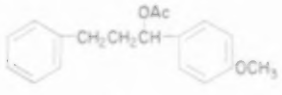
which would perhaps imply that simultaneous O—H bond formation is significant. This is as would be expected for a highly concerted cyclic mechanism.

We next turned our attention to the breaking of the C—O bond. Maccoll[16] has collected relative rate data for the pyrolysis of primary, secondary and tertiary

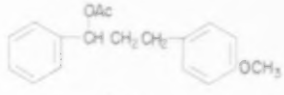
TABLE 1. DEUTERIUM ISOTOPE EFFECT IN THE PYROLYSIS OF 1-METHYLCYCLOHEXYL ACETATE

	Temp °C	% Endo	% Exo	k_H/k_D	k_H/k_D max[13]
1-Methylcyclohexyl acetate	400	73	27		
1-Methylcyclohexyl acetate-d_4	400	59	41	1·9	2·3
1-Methylcyclohexyl acetate	500	73	27		
1-Methylcyclohexyl acetate-d_4	500	61	39	1·7	2·1

acetates and has shown that ethyl, i-propyl and t-butyl acetates react in the ratio 1 : 26 : 1660 at 400°. This is in the order to be expected if heterolytic C—O bond-breaking is important, but as Maccoll has also pointed out, at much reduced relative values than one would expect for a carbonium ion mechanism.[17] It is also the order



II



III

to be expected on statistical, steric and thermodynamic grounds. We have already shown[11] that compound II, a *p*-methoxybenzyl acetate, pyrolyzes only about three times more rapidly than III, again a result inconsistent with the development of appreciable positive charge in the transition state. We have now obtained new results

TABLE 2. RELATIVE RATES OF PYROLYSIS OF ESTERS AT 400°

Compound	Relative rate
5-Nonyl acetate	1
α-Phenylethyl acetate	0·74 ± 0·02[a]
β-Phenylethyl acetate	0·07 ± 0·006[a]
α-Acetoxycyclohexanone	0·06

[a] Corrected for differences in thermal conductivity of the olefins.

which substantiate this conclusion even more thoroughly. The relative rates given in Table 2 were obtained by pyrolyzing mixtures of acetates and determining the ratio of olefinic products by g.p.c. The results were very reproducible, but could only be determined accurately over a small temperature range. They show clearly that the amount of C—O *heterolytic* bond-breaking must be very small, for in any reaction which involved appreciable carbonium ion character the α-phenylethyl acetate would

[16] A. Maccoll, *J. Chem. Soc.* 3398 (1958).
[17] The corresponding bromides pyrolyze to olefins with a rate ratio of 1 : 170 : 32,000.[14]

certainly react much more rapidly than would α-acetoxycyclohexanone. Actually it is only very slightly more reactive. It also suggests that it cannot be true that "it is the forming O—H bond that primarily determines the rate", as concluded by Maccoll,[16] for then β-phenylethyl acetate, with an activated hydrogen to be removed, would be the most reactive of the compounds studied.

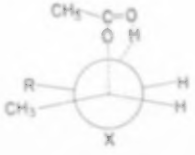
We may then summarize the results in the following way. The carbon–hydrogen bond is being broken in the transition state, as shown by the deuterium isotope effect, but the acidity of the hydrogen being removed is not of primary importance.[18] Substituents at both the carbon bearing the hydrogen and that bearing the acetoxyl exert an influence paralleling that which they will exert on the olefinic product, and consequently, other things being equal,[19] the more stable olefin predominates among the products. It may then be assumed that the transition state of the acetate pyrolysis reaction is best described as being one in which both the C—H and C—O bonds are to a large extent broken and a great deal of double-bond character has developed, but one in which no appreciable charge separation is evident. This then places acetate pyrolysis in a category similar to pyrolyzes of vinyl ethers, as discussed by Maccoll.[16]

With this picture of the transition state firmly in mind, it is possible to predict, with a great deal of accuracy, the ratio of products to be expected in a given pyrolysis. For reasons that will presently become clear, we decided to examine the pyrolysis of 1-methoxyisopropyl acetate. The reaction is that expressed by equation (3), and it is to be compared with the pyrolysis of s-butyl acetate.[5]

$$\underset{\text{IV}}{CH_3O{-}CH_2{-}\underset{\displaystyle OAc}{\underset{|}{CH}}{-}CH_3} \xrightarrow{\Delta} \underset{\text{V}}{CH_3OCH{=}CH{-}CH_3} + \underset{\text{VI}}{CH_3OCH_2CH{=}CH_2} \qquad (3)$$

$$\underset{\text{VII}}{CH_3CH_2\underset{\displaystyle OAc}{\underset{|}{CH}}CH_3} \xrightarrow{\Delta} \underset{\text{VIII}}{\underset{\displaystyle 15\%\ cis}{\underset{\displaystyle 28\%\ trans}{CH_3CH{=}CHCH_3}}} + \underset{\text{IX}}{CH_3CH_2CH{=}CH_2}\ 57\% \qquad (4)$$

Statistically both primary olefins are favored over their internal isomers by a ratio of 3 : 2. The smaller amount of *cis*-2-butene than *trans*-2-butene formed was accounted for on the basis of eclipsing between the two methyl groups in the transition state leading to its formation (Xa). When R = OCH_3 (Xb) such eclipsing may be



(a) R = CH_3
(b) R = OCH_3

slightly diminished and a slight increase in the *cis*/*trans* ratio might be expected, but differences in the two cases on statistical and steric grounds will be small. However,

[18] This last will probably not be true for extremely acidic hydrogens (*vide supra*). If the hydrogen becomes sufficiently acidic the mechanism of the reaction may even change, as it does in the case of xanthate pyrolyses. [F. Bordwell and P. S. Landis, *J. Amer. Chem. Soc.* **80**, 6383 (1958)].
[19] i.e. Statistical and steric effects.

VOL. 7 1959

the methoxyl group will exert its influence by stabilizing the transition state leading to the formation of both *cis* and *trans* V in the same way that it stabilized the olefin in the vinyl ether being formed. Consequently one would predict that a somewhat greater proportion of internal olefins (V) would be formed on pyrolysis of the methoxy acetate than from the pyrolysis of s-butyl acetate. The actual results are in excellent agreement with these predictions, for pyrolysis of IV at 500° gave 47% primary olefin (VI) and 53% internal olefin (V) of which 30% was *trans* and 23% was *cis*. Bailey and Nicholas reported that the product of this pyrolysis was substantially pure primary olefin.[20]

Finally, we conclude our theoretical discussion with a consideration of the effect of temperature on the direction of elimination. Bailey and Hale[6] have pyrolyzed 1-methylcyclohexyl acetate and t-amyl acetate at temperatures from 220° to 600° and have arrived at the conclusion that as the temperature is lowered, Saytzeff elimination is favored, with the Saytzeff product predominating at the lower end of the temperature scale. These results are contrary to our own experience,[5] for we found no appreciable change in product composition as the temperature was lowered. For the deuterium isotope studies reported in this paper we measured the exo–endo product ratio again at 400° and found it to be 73–27, within 1 per cent of its value at 450° and at 500°, and not the 82–18 ratio reported by Bailey and Hale. The same ratio, 73–27, was also found at 350°.[5] We have pyrolyzed t-amyl acetate at 250° and have found no detectable olefinic product, either by g.p.c. or by bromine titration, and by using the Arrhenius parameters given[21] for the pyrolysis of t-butyl acetate it can be calculated that at 225° only 0·0035% yield of olefin would be expected. We therefore believe that another mechanism must be operating in their case at lower temperatures, and may be intruding even at 400°.[22]

With all the current discussion about the mechanistic aspect of the ester pyrolysis reaction, sight may be lost of its synthetic utility. In our experience the reaction is extremely simple, the yields are good and often quantitative, and the products easy to work up. Little charring or other decomposition has been observed. The pyrolysis

(5)

[20] W. J. Bailey and L. Nicholas, *J. Org. Chem.* **21**, 648 (1956). Bailey and Hale[6] say "One could conclude that there are possible at least two sets of experimental conditions for the pyrolysis of esters which give slightly different results in the direction of elimination. One set of conditions appears to give the exocyclic isomer and to proceed in a selective manner according to the Hofmann rule. These highly elusive conditions, however, are not the normal operating conditions and at the present time cannot be defined." Bailey and Hale quote, in support of the above statement, the work of J. G. Traynham and O. S. Pascual, *J. Org. Chem.* **21**, 1362 (1956) who pyrolyzed 1-methylcyclohexyl acetate and who subsequently undoubtedly worked with a product which was at least rich in methylene cyclohexane. They neglect to state, however, that Traynham and Pascual *fractionated their products before use*. Since methylene cyclohexane boils nine degrees lower than 1-methylcyclohexene, it is not unlikely that they had mainly methylene cyclohexane for their further work. We do not believe that there are conditions likely to be found which will lead exclusively to Hofmann or exocyclic products.

[21] C. E. Rudy and P. Fugassi, *J. Phys. Chem.* **52**, 357 (1948).

[22] In this connection it may be significant that Bailey and Hale refer to the paper of W. J. Bailey and J. J. Hewitt, *J. Org. Chem.* **21**, 543 (1956) for the details of how the pyrolyses were carried out. In that paper the pyrolysis tube was cleaned after every run with nitric acid and distilled water. In our experience cleaning after every run is neither necessary nor desirable, but when the helices are cleaned in acid, *they must be washed free of residual acid with ammonia*, for it is not usually possible to wash glass free of acid with water. Traces of residual acid may account for the differences in results found at low temperature.

of α-acetoxycyclohexanone to cyclohexenone (equation 5) is a good example, and this sequence is, in our opinion, competitive with other available methods for the synthesis of this useful intermediate. This general method appears especially attractive for the preparation of higher homologs.

EXPERIMENTAL[23]

1-*Methylcyclohexyl acetate*-2,2,6,6-d_4. Cyclohexanone (49 g, 0·5 mole), D_2O (20 g, 1·0 mole) and K_2CO_3 (0·25 g) were heated at reflux for 24 hr, the solution was cooled and the layers separated. The ketonic layer was mixed with another portion of D_2O and K_2CO_3 and the procedure repeated. After six exchanges the ketone was distilled (30 g) and analyzed for deuterium. It showed 97·0 and 96·5% of the exchange calculated for the replacement of four hydrogens by deuterium. This cyclohexanone (14·3 g, 0·14 mole) was reacted with the Grignard reagent from CH_3I (24·6 g, 0·173 mole) and Mg (4·6 g, 0·19 atom) in 100 ml of dry ether. After working up in the usual manner the deutero 1-methylcyclohexyl alcohol was carefully distilled through a spinning brush column of approximately 15 theoretical plates. The product melted at 27–27·5°. It was acetylated with acetyl chloride and dimethyl aniline.[24] The acetate analyzed for 98% and 97·4% exchange of four hydrogens for deuterium.

Deuterium analyses. These were performed by burning the compound, purifying the water formed and analyzing for per cent deuterium oxide by the falling drop method following the procedure of Kirshenbaum.[25]

5-*Nonyl acetate*. The alcohol, prepared according to the method of *Organic Syntheses*,[26] was acetylated to give the acetate, b.p. 202–204°, lit.[27] 206–207°. It gave only a single peak by g.p.c. analysis.

Phenylethyl acetates. α- and β-phenylethyl acetates were prepared by acetylation of the commercially available alcohols. Their physical properties were in agreement with literature values.

α-*Acetoxycyclohexanone*. This compound was prepared by the method of Shine and Hunt.[28] Recrystallization from pentane gave a product of m.p. 35·5–36° (lit.[4] m.p. 35–36°).

β-*Methoxyisopropyl acetate*. Acetylation of the commercially available alcohol according to the directions of Bailey and Nicholas[29] followed by careful fractionation gave material of b.p. 145–146° (reported,[29] 145·5–146°).

Methyl allyl ether. Allyl bromide (34 g, 0·28 mole) was added dropwise with stirring to a solution of sodium (7·5 g, 0·33 mole) in 250 ml of dry methanol. After heating at reflux for 1 hr the product was distilled from the reaction flask and carefully fractionated. B.p. 42·5–43°, lit.[30] b.p. 42·5–43°.

Pyrolyses. The method and apparatus were as previously described.[5] Peak areas were determined by use of a planimeter. For the competitive pyrolyses equimolar mixtures of the esters and 5-nonyl acetate were passed through the column (for the case of β-phenylethyl acetate the molar ratios were 5 : 1) and the total reaction mixture was analyzed by g.p.c. Conversions were kept low (21–45% of the more reactive olefin) and the relative rates calculated as described by Lee.[31] Prior g.p.c. analysis of an equimolar mixture of pure 4-nonene (from pyrolysis of the acetate) and pure styrene gave a peak area ratio of 1·30 : 1. In the pyrolysis of α-acetoxycyclohexanone no correction was made for differences in thermal conductivity. The relative rates of the phenylethyl acetates are the average for three runs, that for acetoxycyclohexanone for a single run.

Pyrolysis of β-methoxyisopropyl acetate. The acetate was pyrolyzed in the conventional manner at 500° at the rate of 3 ml per min. A conversion of 57% was obtained, as determined by titration of the acetic acid liberated. The olefins were analyzed by g.p.c. The major peak (47%) had a retention time identical to that of an authentic sample of methyl allyl ether. The other two peaks (31% and

[23] Melting and boiling points are uncorrected.
[24] T. D. Nevitt and G. S. Hammond, *J. Amer. Chem. Soc.* **76**, 4124 (1954).
[25] I. Kirshenbaum, *Physical Properties and Analysis of Heavy Water*. McGraw-Hill, New York (1951).
[26] *Organic Syntheses* Coll. Vol. II p. 179. John Wiley, New York (1943).
[27] B. A. Arbuzov and V. S. Vinogradova, *Bull. Acad. Sci. U.S.S.R.* 535 (1954).
[28] H. J. Shine and G. E. Hunt, *J. Amer. Chem. Soc.* **80**, 2434 (1958).
[29] A. A. Petrov, *J. Gen. Chem. U.S.S.R.* **14**, 1038 (1944).
[30] J. Irvine, J. MacDonald and C. Soutar, *J. Chem. Soc.* **107**, 351 (1951).
[31] T. S. Lee in *Techniques of Organic Chemistry* Vol. VIII, p. 101. Interscience Publishers, New York (1953).

22% respectively) were assigned to the *trans* and *cis* enol ether because a sample of the pyrolysate with 2,4-dinitrophenylhydrazine solution formed an immediate copious precipitate of the 2,4-dinitrophenylhydrazone of propionaldehyde, m.p. 153·5–154·5°, (reported[32] m.p. 155°). It was assumed that the larger peak, with the smaller retention volume, was the *trans* isomer by analogy with the butenes.

Pyrolysis of α-acetoxycyclohexanone. The pyrolysis was carried out in the conventional manner at 510°. The rate of addition was 0·5 ml per min and a conversion of 96% was obtained. The product was identified as cyclohexenone by its infrared spectrum and its retention volume on gas chromatography.

[32] C. Allen, *J. Amer. Chem. Soc.* **52**, 2957 (1930).

VOL. 7 1959

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16-SUBSTITUTED STEROIDS

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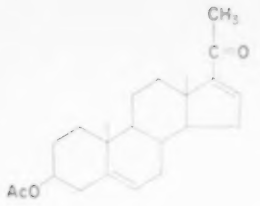
Abstract—The reactions of 3β-acetoxy-5,16-pregnadien-20-one with cyanide ion and with certain active methylene compounds are described. Subsequent transformations of the initial products to give various 16-substituted pregnenolones and progesterones are shown.

THE recent publication by Romo[1] of the addition of hydrocyanic acid to 16-pregnen-20-ones prompted us to record our own results with this and related reactions.[2] We have found that not only does 16-dehydropregnenolone acetate add hydrocyanic acid but that it also behaves as a typical α, β-unsaturated ketone in the Michael reaction. Thus, in the presence of strong alkali, we have prepared adducts with ethyl cyanoacetate, malononitrile, ethyl malonate,[3] ethyl acetoacetate and acetylacetone. The adducts were shown to be 16-substituted pregnenolones by infrared and ultraviolet spectra which demonstrated the presence of the 20-ketone and the absence of the conjugated Δ^{16}-20-ketone respectively.

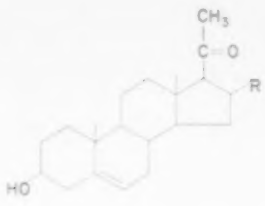
The addition of hydrocyanic acid to 16-dehydropregnenolone acetate (I) was carried out essentially as described by Romo[1] and 16α-cyano-3β-hydroxy-5-pregnen-20-one (II) was obtained. Michael reactions with I were run by two general methods. The first used ethanol as solvent and sodium ethoxide as the base. In this manner were obtained adducts III and IV with ethyl cyanoacetate and malononitrile respectively. Concomitant saponification of the 3-acetate took place. The second method used excess addend as solvent and preformed sodium enolate of the addend as base. The latter procedure yielded adducts V, VI and VII with ethyl malonate, ethyl acetoacetate and acetylacetone respectively. It should be noted that in the absence of solvent alcohol no saponification of the 3-acetate occurred. It was found possible to saponify III under mild conditions to the corresponding acid which was thermally decarboxylated yielding 16α-cyanomethyl-3β-hydroxy-5-pregnen-20-one (VIII), in effect the adduct of 16-dehydropregnenolone and acetonitrile. Oppenauer oxidation of adducts II, III, IV and VIII to the corresponding 16-substituted progesterones, IX, X, XI and XII, was straightforward and uniformly successful.

Some further transformations of 16α-cyanopregnenolone (II) were effected. Reduction of II with sodium borohydride gave 16α-cyano-5-pregnene-3β, 20β-diol (XIII) from which the diacetate XIV was prepared. The diol XIII was oxidized selectively to 16α-cyano-20β-hydroxy-4-pregnen-3-one (XV) by Oppenauer oxidation for a short time. Vigorous alkaline hydrolysis of diol XIII gave two products, a result of the expected epimerization at C-16 under the reaction conditions. The first was 16β-carboxy-5-pregnene-3β, 20β-diol 16, 20-lactone (XVII) characterized as the acetate

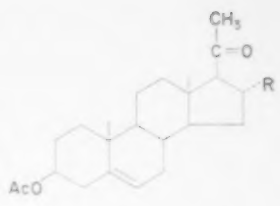
[1] J. Romo, *Tetrahedron* **3**, 37 (1958).
[2] R. H. Mazur, U.S. Pat. 2, 817, 671 (Dec. 24, 1957).
[3] P. Bladon, *J. Chem. Soc.* 3723 (1958).



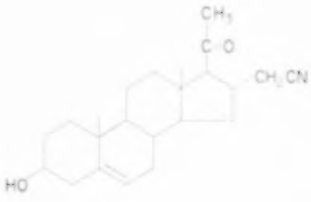
I



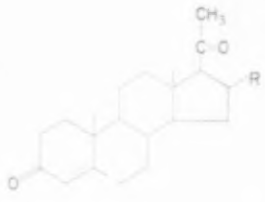
II R=CN
$CO_2C_2H_5$
III R=CHCN
IV R=CH(CN)$_2$



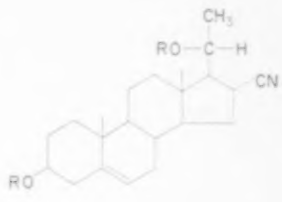
V R=CH($CO_2C_2H_5$)$_2$
$CO_2C_2H_5$
VI R=CHCOCH$_3$
VII R=CH(COCH$_3$)$_2$



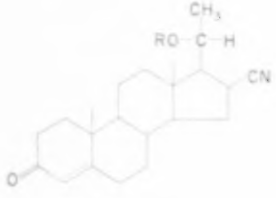
VIII



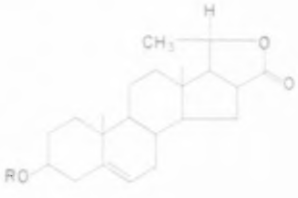
IX R=CN
$CO_2C_2H_5$
X R=CHCN
XI R=CH(CN)$_2$
XII R=CH_2CN



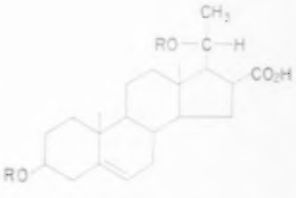
XIII R=H
XIV R=Ac



XV R=H
XVI R=Ac



XVII R=H
XVIII R=Ac



XIX R=H
XX R=Ac

XVIII and the second 16α-carboxy-5-pregnene-3β, 20β-diol (XIX) characterized as the diacetate XX. Compound XVII was never obtained as the hydroxyacid, lactonization being spontaneous. The configurations of XVII and XIX seem clear since such ready lactonization as XVII exhibits can only take place if the product has the two five-membered rings *cis*-fused. Oppenauer oxidation of XVII gave 16β-carboxy-20β-hydroxy-4-pregnen-3-one 16,20-lactone (XXI). The diacetate XX was saponified with two equivalents of sodium hydroxide, the resultant mixture (both XIX and the 20-monoacetate subsequently proved to be present) esterified with diazomethane and the crude esters subjected to Oppenauer oxidation. By a circuitous isolation procedure, very low yields of 20β-acetoxy-16α-carboxy-4-pregnen-3-one (XXII) and 16α-carbomethoxy-20β-hydroxy-4-pregnen-3-one (XXIII) were eventually obtained.

The assignment of the 20β-configuration to the diol XIII is based on molecular

rotation differences.[4,5] It may be seen from Table 1 that the molecular rotation changes upon acetylation of XIII to XIV and of XV to XVI are in agreement with the literature values for the acetylation of the corresponding 20β-hydroxy compounds without substituents at C-16.

A particularly interesting feature of the 1,4-addition reactions of 16-dehydropregnenolone acetate is that of stereochemistry. Previous chemists[6–11] have assumed the adducts to have the substituents in the 16α, 17β configuration (i.e. with a normal

TABLE 1

Compound	M_D	ΔM_D
5-Pregnene-3β,20α-diol[a]	−170	
5-Pregnene-3β,20α-diol diacetate	−216	−46
5-Pregnene-3β,20β-diol	−204	
5-Pregnene-3β,20β-diol diacetate	−145	+59
XIII[b]	−250	
XIV	−239	+11
20α-Hydroxy-4-pregnen-3-one	+312	
20α-Acetoxy-4-pregnen-3-one	+312	0
20β-Hydroxy-4-pregnen-3-one	+286	
20β-Acetoxy-4-pregnen-3-one	+462	+176
XV	+164	
XVI	+318	+154

[a] The reference compounds are described by R. B. Turner and D. M. Voitle, *J. Amer. Chem. Soc.* **73**, 2283 (1951). The rotations were measured in chloroform solution. [b] The rotations of XIII–XVI were measured in dioxane solution.

rather than an iso side chain at C-17), an assignment which follows from the approach of the anion on the least hindered side of the molecule. We feel there is little reason to doubt this interpretation of the reaction. In the present work, also, the substituents at C-16 very probably have the 16α configuration although the molecular rotation changes are erratic and permit no definite conclusions. A further complicating factor in compounds III and VI is the introduction of a new asymmetric centre in the side chain. That none of the adducts has a 16α,17α or 16β,17α configuration is shown, we feel, by the fact that not one product has a negative rotation. Additionally, oxidation of our 16-substituted pregnenolones yielded 16-substituted progesterones showing large positive specific rotations but not substances having low specific rotations. As it is known that 3β-hydroxy-5α,17α-pregnan-20-one[12] and 3β-hydroxy-17α-pregn-5-en-20-one[13] have large negative specific rotations while 17α-pregn-4-ene-3,20-dione (17-isoprogesterone)[14] has a zero rotation, it seems quite certain that

[4] L. F. Fieser and M. Fieser, *Experientia* **4**, 285 (1948).
[5] L. H. Sarett, *J. Amer. Chem. Soc.* **71**, 1175 (1949).
[6] D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 196 (1951).
[7] J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *J. Amer. Chem. Soc.* **73**, 1528 (1951).
[8] H. Hirschmann, E. B. Hirschmann and M. A. Daus, *J. Amer. Chem. Soc.* **74**, 539 (1952).
[9] D. Gould, F. Gruen and E. B. Hershberg, *J. Amer. Chem. Soc.* **75**, 2510 (1953).
[10] G. P. Mueller and B. Riegel, *J. Amer. Chem. Soc.* **76**, 3686 (1954).
[11] D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen and E. B. Hershberg, *J. Amer. Chem. Soc.* **78**, 3158 (1956).
[12] C. W. Shoppee, *J. Chem. Soc.* 1671 (1949).
[13] A. Butenandt and G. Fleischer, *Ber.* **70**, 96 (1937).
[14] A. Butenandt, J. Schmidt-Thomé and H. Paul, *Ber.* **72**, 1112 (1939).

the substances prepared by anionic addition to 16-dehydropregnenolone acetate have 17β side chains.[15] It can of course be argued that introduction of a new asymmetric centre at C-16 vitiates any conclusions which may be drawn from unsubstituted steroids. However, it would be most amazing if a vicinal effect could completely nullify the very large 17-iso shift. For example, were 16-cyanopregnenolone to be, in fact, 16-cyano-17-isopregnenolone, introduction of the cyano group (whether α or β) would require a molecular rotary shift of around +500°.

An additional interesting aspect is that a 16-substituted pregnenolone *was* obtained[1,16] having a large negative specific rotation and yielding a 16-substituted progesterone having a low positive specific rotation. Further, these compounds were prepared[1] under conditions known[12,13] to isomerize the 17β-to the 17α-acetyl side chain. Specifically, strong alkaline hydrolysis[1] of 16α-cyanopregnenolone gave a 16-carboxypregnenolone with an attendant molecular rotatory shift of −463° (compare the change XIV to XX with ΔM_D +3°). Similar hydrolysis[1] of 16α-cyanoprogesterone produced a 16-carboxyprogesterone and a molecular rotatory shift of −479°.[17] We feel this typical rotatory shift indicates that isomerization at C-17 has occurred and we believe that inversion at C-16 has happened also. Reduction[1] of 3β-acetoxy-16β-carbomethoxy-17α-pregn-5-en-20-one (XXV) with sodium borohydride and subsequent alkaline saponification yielded 16β-carboxy-17α-pregn-5-ene-3β,20-diol (XXVI). The latter could not be induced to cyclize even under forcing conditions. Romo[1] interpreted this result as proving that the 16-carboxyl and *20-hydroxyl* were *trans*. Rather, failure to cyclize means that the 16-carboxyl and 17-hydroxy-ethyl *side-chain* are *trans*. If we assume the side chain to have the 17α configuration, then the carboxyl group must be 16β. The most likely reaction during which the group at C-16 could have isomerized is saponification of the nitrile. Thus, the alkaline saponification[1] of 16α-cyanopregnenolone and 16α-cyanoprogesterone very likely gave 16β-carboxy-3β-hydroxy-17α-pregn-5-en-20-one (XXIV) and 16β-carboxy-17α-pregn-4-ene-3,20-dione (XXVIII) respectively.

We may say in general that at equilibrium the configuration of a 16-substituted 20-ketopregnane is determined by the steric requirements of the group at C-16. Under alkaline conditions, one obtains 16α-cyanopregnenolone but 16β-carboxy-17-isopregnenolone. Thus, the linear cyano group can be accommodated in the 16α position giving the product expected from backside attack on ring D. However, the preferred orientation of the bulkier carboxyl group is apparently 16β leading (in the presence of an easily epimerizable acetyl group) to the 17α-acetyl side chain which latter arrangement is associated with less steric hindrance among the groups at C-13, 16 and 17.

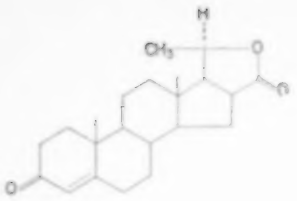
A coincidence is exhibited by XX and the substance XXVII to which Romo[1] assigned the same structure but which most likely has the opposite configuration at both C-16 and C-17. The two compounds differ greatly in melting point but have

[15] As a point of internal consistency, 3β-hydroxy-5α,17α-pregnan-20-one, 3β-hydroxy-17α-pregn-5-en-20-one and 17-isoprogesterone show large negative and approximately equal molecular rotatory shifts relative to the appropriate 17β (normal) isomers. The values of ΔM_D(17α-17β) are −532°, −533° and −605° respectively.

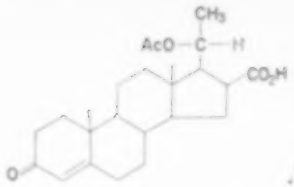
[16] B. Ellis, V. Petrow and D. Wedlake, *J. Chem. Soc.* 3748 (1958). These authors also studied the reaction of potassium cyanide with 16-dehydropregnenolone and hydrolysis of the resulting 16-cyanopregnenolone. They obtained, among others, compounds II, XXIV and XXVIII and assigned the same structures as did Romo.[1] The arguments in the present paper, therefore, apply equally to the results of Ellis *et al.*

[17] The same substance was obtained by Oppenauer oxidation of the above 16-carboxypregnenolone.[1]

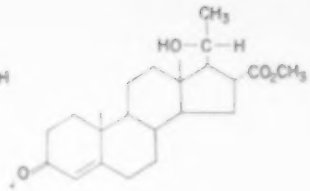
VOL. 7 1959



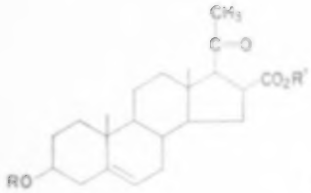
XXI



XXII

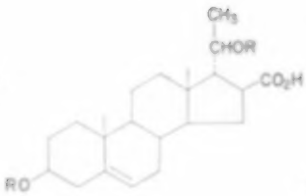


XXIII



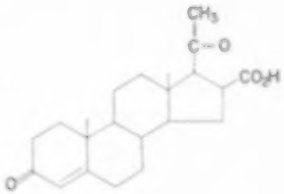
XXIV R = R' = H

XXV R = Ac, R' = CH_3



XXVI R = H

XXVII R = Ac



XXVIII

nearly identical rotations. The changes in molecular rotation for the steps II → XIII → XX and II → XXIV → XXVI → XXVII are shown in Table 2. The large negative shift in the reduction of II to XIII is in accord with other reductions of 20-keto-17β-pregnanes.[4,5] The large negative molecular rotatory shift caused by the hydrolysis of II to XXIV already has been shown to be due principally to inversion at C-17. The moderately large positive shift associated with the conversion of XXIV to XXVI may prove to be generally typical of the reduction of a 20-keto-17α-pregnane. At present, there are no other examples in the literature of 20-hydroxy compounds in the 17α series (without an oxygen function at C-17 also). The positive change in molecular rotation upon acetylation of XXVI to XXVII may indicate that XXVI has a 20β-hydroxyl group, but the lack of suitable models prevents a definite assignment of configuration.

TABLE 2

Compound	M_D[a]	ΔM_D[d]
II	+78 (M),[b] +48 (C)[c]	
IX	+540 (C)[c]	
XIII	−250 (D)[b]	−328 (II M)
XX	−236 (D)[b]	+14 (XIII)
XXIV	−415 (C)[c]	−463 (II C)
XXVI	−306 (D)[c]	+109 (XXIV)
XXVII	−239 (C)[c]	+67 (XXVI)
XXVIII	−61 (C)[c]	−479 (IX)

[a] The solvent for rotation measurement is indicated by C = chloroform, D = dioxane and M = methanol. [b] Present work. [c] Reference 1. [d] The numeral in parentheses shows the reference compound.

VOL. 7 1959

EXPERIMENTAL[18]

16α-Cyano-3β-hydroxy-5-pregnen-20-one (II). 16-Dehydropregnenolone acetate (20·2 g, 0·057 mole) and 20 g (0·31 mole) potassium cyanide were suspended in 400 ml methanol, 40 ml ethyl acetate and 40 ml water. The mixture was heated at the reflux temp for 2 hr during which time a clear solution resulted. Dilution with 500 ml water and cooling yield 17·1 g crude product. Crystallization from benzene–ethanol by concentrating to remove ethanol gave 13·2 g (68%) needles, m.p. 225–228°. Recrystallization from butyl acetate raised the m.p. to 231–234°; $[\alpha]_D$ +23° (*c* 0·5, methanol) (Found: C, 77·49; H, 8·97; N, 4·04. Calc. for $C_{22}H_{31}NO_2$: C, 77·38; H, 9·15; N, 4·10%).

16α-(α-Carbethoxycyanomethyl)-3β-hydroxy-5-pregnen-20-one (III). To a solution of 14 g (0·6 mole) sodium in 1 l. dry ethanol was added 68 g (0·6 mole) ethyl cyanoacetate and 107 g (0·3 mole) 16-dehydropregnenolone acetate. The mixture was stirred until solution occurred (ca. 1½ hr) and allowed to stand overnight at room temp. The solution was neutralized with acetic acid, diluted with chloroform and washed with dil HCl and water until no further color was extracted. The residue from distillation of the chloroform yielded 34 g crude III on trituration with ethyl acetate. Crystallization of this crude product from ethyl acetate gave 27·0 g tiny needles, m.p. 198–200°. The combined mother liquors were chromatographed on silica gel. Elution with 20% ethyl acetate–benzene and subsequent crystallization from ethyl acetate gave an additional 31·0 g of the desired product, m.p. 196–198°; yield, 58·0 g (45%); $[\alpha]_D$ +18° (*c* 1·0, methanol) (Found: C, 72·93; H, 8·51; N, 3·23. $C_{26}H_{37}NO_4$ requires: C, 73·03; H, 8·72; N, 3·28%).

16α-Dicyanomethyl-3β-hydroxy-5-pregnen-20-one (IV). The above procedure was followed using 1·4 g (0·06 mole) of sodium, 4·0 g (0·06 mole) malononitrile and 10·7 g (0·03 mole) 16-dehydropregnenolone acetate. The crude product was chromatographed on silica gel. Elution with 20% ethyl acetate–benzene and crystallization of the material thus obtained from benzene gave 3·8 g (33%), m.p. 203–207°. Recrystallization from 95% ethanol raised the m.p. to 206–209°; $[\alpha]_D$ 0° (*c* 1·0, chloroform) (Found: C, 75·78; H, 8·63; N, 7·10. $C_{24}H_{32}N_2O_2$ requires: C, 75·75; H, 8·48; N, 7·36%).

3β-Acetoxy-16α-dicarbethoxymethyl-5-pregnen-20-one (V). To 1·5 g (0·065 mole) sodium in 100 ml diethyl malonate was added a suspension of 17·8 g (0·05 mole) 16-dehydropregnenolone acetate in 100 ml diethyl malonate. The steroid was dissolved by brief warming and the solution allowed to stand overnight at room temp. The solution was acidified with acetic acid, diluted with ether and washed well with water. Distillation of the organic solvents left a solid residue which was chromatographed on silica gel. Elution with 10% ethyl acetate–benzene yielded 14·1 g crude material from which was obtained by two crystallizations from 70% ethanol 9·0 g (35%) of the desired product, m.p. 122–124°; $[\alpha]_D$ +43° (*c* 0·9, dioxane) (Found: C, 69·86; H, 8·54. $C_{30}H_{44}O_7$ requires: C, 69·74; H, 8·58%).

3β-Acetoxy-16α-(α-carbethoxyacetylmethyl)-5-pregnen-20-one (VI). The above procedure with identical quantities was followed except that ethyl acetoacetate was substituted for diethyl malonate. The desired product was eluted from silica gel with 10% ethyl acetate–benzene. Crystallization from methanol gave VI, 12·7 g (52%), m.p. 163–167°. Recrystallization from isopropyl ether raised the m.p. to 165–167°; $[\alpha]_D$ +28° (*c* 1·1, dioxane) (Found: C, 71·50; H, 8·59. $C_{29}H_{42}O_6$ requires: C, 71·57; H, 8·70%).

3β-Acetoxy-16α-diacetylmethyl-5-pregnen-20-one (VII). The above procedure was repeated using acetylacetone in place of ethyl acetoacetate. Trituration of the crude product with methanol resulted in the recovery of 11·0 g of starting material. Chromatography of the remainder and elution with 10% ethyl acetate–benzene yielded after crystallization from ethanol, 0·80 g (9%) of VII, m.p. 182–186°; $[\alpha]_D$ +86° (*c* 1·0, dioxane) (Found: C, 73·71; H, 8·72. $C_{25}H_{36}O_5$ requires: C, 73·68; H, 8·77%).

16α-Cyanomethyl-3β-hydroxy-5-pregnen-20-one (VIII). Adduct III (10·6 g, 0·025 mole) and 1·7 g (0·03 mole) potassium hydroxide in 106 ml dioxane and 30 ml water were heated on the steam bath for 45 min. The solution was acidified with acetic acid, diluted with water and concentrated to remove most of the dioxane. The product was extracted with chloroform. Distillation of the chloroform gave the cyanoacetic acid derivative, m.p. ca. 240° with gas evolution. The crude acid was decarboxylated by heating at 275–300° until carbon dioxide evolution ceased (ca. ½ hr). Crystallization of the residue from ethyl acetate yielded small needles, 8·3 g (94%), m.p. 202–204°. Recrystallization from ethyl

[18] We would like to thank Robert T. Dillon and associates for analyses. Melting points are uncorrected. Rotations were determined at 25 ± 3°. Ultraviolet spectra were carried out in methanol.

acetate raised the m.p. to 206–207°; $[\alpha]_D$ +14° (*c* 1·1, chloroform) (Found: C, 77·64; H, 9·03; N, 3·88. $C_{23}H_{33}NO_2$ requires: C, 77·70, H, 9·36; N, 3·94%).

Oppenauer oxidations. The general procedure followed was to dissolve the compound in 40–50 vol toluene and 5 vol freshly redistilled cyclohexanone. Five vol 20% aluminum isopropoxide in toluene were added and the solution heated under reflux for 2 hr. To the cooled solution was added an equal vol of 50% aqueous potassium sodium tartrate and the organic solvents removed by extensive steam distillation. The product was extracted with benzene, chromatographed on silica gel and eluted with 10% ethyl acetate–benzene.

Adduct II (2·98 g) gave 16α-*cyanoprogesterone* (IX), 1·72 g (57%), prisms from aqueous methanol, m.p. 230–233°; $[\alpha]_D$ +151° (*c* 0·5, methanol); λ_{max} 240 mμ, ε = 17,300 (Found: C, 77·89; H, 8·54; N, 4·07. Calc. for $C_{22}H_{29}NO_2$: C, 77·83; H, 8·61; N, 4·13%).

Adduct III (3·24 g) gave 16α-(α-*carbethoxycyanomethyl*)-*progesterone* (X), 1·22 g (37%), needles from ethyl acetate–cyclohexane, m.p. 213–216°; $[\alpha]_D$ +103° (*c* 0·5, methanol); λ_{max} 240 mμ, ε = 16,500 (Found: C, 73·41; H, 8·22; N, 3·29. $C_{26}H_{35}NO_4$ requires: C, 73·38; H, 8·29; N, 3·29%).

Adduct IV (1·75 g) gave 16α-*dicyanomethylprogesterone* (XI), 1·11 g (64%), prisms from benzene–cyclohexane, m.p. 206–210°; $[\alpha]_D$ +112° (*c* 1·0, chloroform); λ_{max} 240 mμ, ε = 16,300 (Found: C, 76·40; H, 7·99; N, 6·93. $C_{24}H_{30}N_2O_2$ requires: C, 76·15; H, 7·99; N, 7·40%).

Adduct VIII (52·0 g) gave 16α-cyanomethylprogesterone (XII), 31·3 g (60%), prisms from benzene–cyclohexane, m.p. 185–186°; $[\alpha]_D$ +142° (*c* 0·5, methanol); λ_{max} 240 mμ, ε = 16,300 (Found: C, 78·35; H, 8·95; N, 4·02. $C_{23}H_{31}NO_2$ requires: C, 78·13; H, 8·84; N, 3·96%).

16α-*Cyano*-5-*pregnene*-3β,20β-*diol* (XIII). Cyanopregnenolone II (6·0 g 0·0175 mole) was dissolved in 100 ml hot ethanol. Sodium borohydride (1·5 g) in 15 ml water was added and the solution warmed on the steam bath for ½ hr. The solution was acidified with acetic acid and concentrated to a small vol yielding 5·0 g (83%) XIII, m.p. 224–228°. Crystallization from methanol raised the m.p. to 231–233°; $[\alpha]_D$ −73° (*c* 0·5, dioxane) (Found: C, 76·78; H, 9·54. $C_{23}H_{33}NO_2$ requires: C, 76·92; H, 9·68%).

The *diacetate* XIV, m.p. 212–213° (methanol), was prepared by brief refluxing of XIII with pyridine and acetic anhydride; $[\alpha]_D$ −56° (*c* 0·5, dioxane) (Found: C, 72·99; H, 8·52. $C_{28}H_{37}NO_4$ requires: C, 73·03; H, 8·72%).

16α-*Cyano*-20β-*hydroxy*-4-*pregnen*-3-*one* (XV). The general procedure for Oppenauer oxidations was used except that the solution was heated under reflux for only 10 min. The crude material from 2·0 g XIII was chromatographed on silica gel. Elution with 25% ethyl acetate–benzene and subsequent crystallization from benzene gave the desired product, 0·41 g (20%), m.p. 215–219°; $[\alpha]_D$ +48° (*c* 1·0 dioxane); λ_{max} 240·5 mμ, ε = 16,500 (Found: C, 77·33; H, 8·83. $C_{23}H_{31}NO_2$ requires: C, 77·37; H, 9·15%).

The *acetate* XVI, m.p. 217–218° (methanol), was prepared by treatment with acetic anhydride in pyridine overnight at room temp; $[\alpha]_D$ +83° (*c* 1·0 dioxane); λ_{max} 240 mμ, ε = 17,200 (Found: C, 75·17; H, 8·69; N, 3·51. $C_{24}H_{33}NO_3$ requires: C, 75·16; H, 8·67; N, 3·65%).

Saponification of XIII. 16α-Cyano-5-pregnene-3β,20β-diol (38·0 g, 0·11 mole) in 1 l. of 95% ethanol was treated with 200 g potassium hydroxide in 500 ml water and the solution heated under reflux for 3 days. Acidification of the cooled solution with HCl gave a gelatinous product. The crude material was acetylated by heating with pyridine and acetic anhydride and the mixture of acetates chromatographed on silica gel. Elution with 5% ethyl acetate–benzene yielded, after crystallization from ethanol, 8·5 g (20%) of 3β-*acetoxy*-20β-*hydroxy*-5-*pregnen*-16β-*carboxylic acid* 16,20-*lactone* (XVIII), m.p. 238–240°; $[\alpha]_D$ −35° (*c* 1·0, dioxane); λ_{max}^{KBr} 5·67, 5·81 μ (Found: C, 74·52; H, 8·88. $C_{24}H_{34}O_4$ requires: C, 74·58; H, 8·87%).

Alkaline hydrolysis of XVIII yielded, after acidification to reclose the lactone, 16β-*carboxy*-5-*pregnene*-3β,20β-*diol* 16,20-*lactone* (XVII), m.p. 241–243° from ethyl acetate; $[\alpha]_D$ −31° (*c* 0·6, dioxane) (Found: C, 76·47; H, 9·76. $C_{22}H_{32}O_3$ requires: C, 76·70; H, 9·34%).

Elution of the column with 10% ethyl acetate–benzene and subsequent crystallization from ethyl acetate–cyclohexane gave 14·0 g (29%) of 3β,20β-*diacetoxy*-5-*pregnene*-16α-*carboxylic acid* (XX), m.p. 184–185°; $[\alpha]_D$ −53° (*c* 0·8, dioxane) (Found: C, 69·92; H, 8·53. $C_{28}H_{38}O_6$ requires: C, 69·92; H, 8·85%).

Saponification of XX resulted in 16α-*carboxy*-5-*pregnene*-3β,20β-*diol* (XIX), m.p. 289–293° from ethanol (Found: C, 71·35; H, 9·40. $C_{22}H_{34}O_4$·½C_2H_5OH requires: C, 71·65; H, 9·67%).

16β-*Carboxy*-20β-*hydroxy*-4-*pregnen*-3-*one* 16,20-*lactone* (XXI). Oppenauer oxidation of XVII

by the general procedure described above—except that the solution was heated under reflux for 15 min—yielded the desired product after chromatography on silica gel and elution with 20% ethyl acetate–benzene. From 0·90 g XVII was obtained 0·55 g (60%) XXI, m.p. 188–190° from ethyl acetate–petroleum ether (b.p. 60–80°); $[\alpha]_D$ +96° (*c* 1·0, dioxane); λ_{max} 241 mμ, ε = 17,000 (Found: C, 77·49; H, 8·97. $C_{22}H_{30}O_3$ requires: C, 77·15; H, 8·83%).

20β-Acetoxy-16α-carboxy-4-pregnen-3-one (XXII) *and 16α-carbomethoxy-20β-hydroxy-4-pregnen-3-one* (XXIII). Compound XX (4·46 g, 0·01 mole) was allowed to stand overnight at room temp with a solution of 0·46 g (0·02 mole) sodium in 200 ml 90% ethanol. The solution was concentrated to a small vol, diluted with water and acidified with HCl. The voluminous precipitate was collected by filtration, washed with water and dried. The crude product was suspended in 30 ml dioxane and esterified with ethereal diazomethane. The resultant solution was concentrated to dryness and oxidized directly by the usual Oppenauer procedure with the reaction time limited to 15 min. The crude product was chromatographed on silica gel. The material eluted with 10% ethyl acetate–benzene was saponified with aqueous methanolic sodium hydroxide, acetylated with acetic anhydride in pyridine and rechromatographed on silica gel to yield 20β-acetoxy-16α-carboxy-4-pregnen-3-one (XXII), 0·25 g, m.p. 239–243°, from ethyl acetate–isopropyl ether; $[\alpha]_D$ +66° (*c* 0·5, dioxane); λ_{max} 241, ε = 16,400 (Found: C, 71·75; H, 8·66. $C_{24}H_{34}O_5$ requires: C, 71·61; H, 8·51%).

The fraction eluted from the original column with 30% ethyl acetate–benzene gave 16α-carbomethoxy-20β-hydroxy-4-pregnen-3-one (XXIII), 0·05 g, m.p. 144–146° from petroleum ether (b.p. 60–80°); $[\alpha]_D$ +31° (*c* 1·0, dioxane); λ_{max} 241, ε = 15,700 (Found: C, 73·81; H, 9·26. $C_{23}H_{34}O_4$ requires: C, 73·75; H, 9·10%).

VOL. 7 1959

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STEROIDS—CXX[1] SYNTHESIS OF HALOGENATED STEROID HORMONES

NEW ROUTES TO 6α-FLUOROTESTOSTERONE AND THE 6α- AND 6β-FLUORO ANALOGS OF PROGESTERONE. THE SYNTHESIS OF 6α- AND 6β-FLUORO REICHSTEIN'S COMPOUND "S" AND 6α- AND 6β-FLUORODESOXYCORTICOSTERONE ACETATE[2]

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Abstract—The conformational and electronic factors involved in the fission of steroid 5α,6α-epoxides with boron trifluoride-etherate are discussed with particular reference to C-3-keto-5α,6α-epoxides and their cycloethylene-dioxy derivatives.

These considerations led to the development of a new synthesis of 6-fluoro-Δ^4-3-ketones from the corresponding Δ^4-3-ketones via the boron trifluoride-etherate cleavage of their derived cycloethylene-ketal-5α,6α-epoxides.

Application of this method led to the synthesis of 6α-fluorotestosterone and the 6α and 6β-fluoro analogs of progesterone desoxycorticosterone acetate and Reichstein's Compound "S" diacetate. The latter compound and its Δ^1-analog are valuable precursors for the 6-fluoro cortical hormones.

Recently we described methods leading to the synthesis of the 6α- and 6β-fluoro analogs of testosterone and progesterone.[3] The introduction of the fluorine atom involved the rupture of a 3β-hydroxy-5α,6α-epoxide (or its derived acetate) with boron trifluoride etherate[3,4] to afford the corresponding 5α-hydroxy-6β-fluoro compound, (Fig. 1; I → II). In every case the precursor for the epoxide was the appropriate Δ^5-3β-alcohol. Although these compounds are readily accessible in most series, the synthesis of 6-fluorocortisone, for example, by application of this general method would necessitate as a precursor the Δ^5-3β-alcohol (III). However, such an intermediate is not readily available, and for this and other reasons it was desirable to develop alternate routes to 6-fluoro-Δ^4-3-ketones which could eventually be utilized for the synthesis of the C-6-fluoro-cortical hormones.

The fission of a steroid 5α,6α-epoxide with boron trifluoride has been shown to afford either the C-6 ketone (rings A/B *cis*) (Fig. 1; IV → V) or the diaxial 5α-hydroxy-6β-fluoro compound (I → II) depending upon the nature and stereochemistry of the substituent at C-3.[3,4] An epoxide unsubstituted at C-3 (IVa) or carrying a 3α-acetoxyl group (IVb) affords as the major product the corresponding C-6 ketone (V).[4] However, a 3β-hydroxy-epoxide (or its acetate ester) (I) undergoes fission by a completely different mechanism, and the major product is the fluorohydrin (II).[3,4]

Henbest and Wrigley[4] explained these results from a consideration of the electronic

[1] Part CXIX: J. A. Zderic, H. Carpio and C. Djerassi, *J. Org. Chem.* **24**, 909 (1959).
[2] Presented in part by A.B. at the Steroids and Natural Products Section of the Gordon Research Conference, August 1958.
[3] A. Bowers and H. J. Ringold, *Tetrahedron* **3**, 14 (1958).
[4] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4765 (1957).

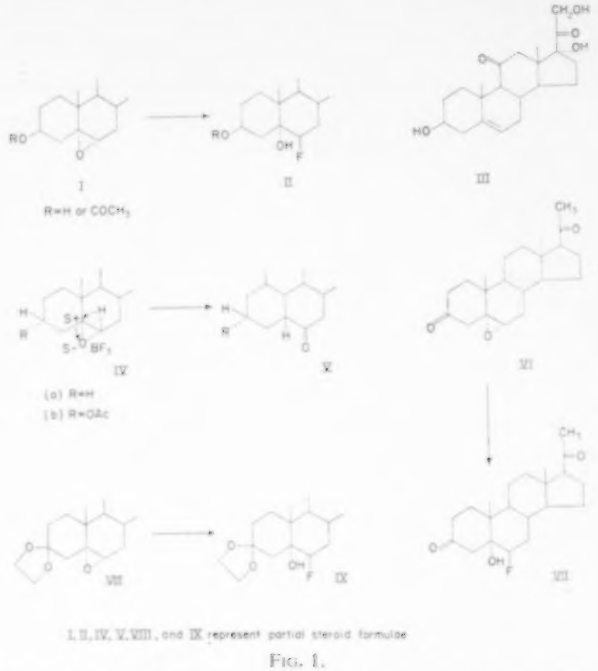

FIG. 1.

and the conformational factors involved. In the unsubstituted epoxide, boron trifluoride induces partial ionization of the bond from the epoxide oxygen to the more alkylated C-5 position, promoting a concerted 1,2-hydride shift with concomitant formation of the C-6 ketone (A/B-*cis*) (IV → V).

However, in the case of a 3β-alcohol or its ester two factors oppose the formation of the C-6 ketone. Firstly, the partial ionization of the epoxide oxygen-C-5 bond (necessary for C-6 ketone formation) is reduced by the magnified inductive effect (—I) of the boron-trifluoride co-ordinated C-3(β) alcohol or ester. Secondly, the formation of a C-6 ketone (rings A/B *cis*) would markedly increase the non-bonded interactions in ring A, for the 3β-hydroxyl group would then be axially orientated Thus, an alternative, secondary reaction leading to fluorohydrin formation predominates.

In the case of a 3α-acetate (axial)-5α,6α-epoxide (IVb) the electronic and conformational factors are in direct opposition, but the —I effect of the axial acetate group is not sufficient to overcome (a) the gain in energy resulting from the axial acetate group assuming an equatorial conformation upon C-6 ketone formation, and (b) the unfavorable 1,3-diaxial interaction (3α,5α-diol) which would result if fluorohydrin formation occurred. The net result is the formation of the C-6 ketone in very high yield.

In an attempt to assess the relative importance of the electronic factors, we studied the fission of a C-3-keto-5α,6α-epoxide with boron trifluoride. In this system the conformational factors outlined above which influenced the fission of both the 3α-acetoxy and the 3β-acetoxy epoxides are absent, and it is the balance between the boron trifluoride induced ionization of the C-5-epoxide oxygen and its inhibition by the —I effect of the ketone which determines the course and products of the

reaction. The inductive influence clearly predominated since treatment of 5α,6α-oxidopregnan-3,20-dione (VI)[5] with boron trifluoride-etherate afforded in 44 per cent yield the fluorohydrin (VII), identical with an authentic specimen.[3] This result indicated that fluorohydrin formation should be the major reaction for 5α,6α-epoxides which are substituted at C-3 by a group which (after co-ordination with boron trifluoride) will exert a reasonably strong —I effect, and in which there are no powerful conformational factors in opposition.

With this information available, we considered that a 3-cycloethylene-ketal-5α,6α-epoxide (VIII) should be a suitable substrate for conversion into a fluorohydrin. After coordination with two molecules of electron deficient boron trifluoride, it would be a reasonably strong —I group, and its symmetrical nature about C-3 would eliminate such conformational factors as an axial group becoming equatorial, and vice versa. This conclusion was verified experimentally. In four series investigated a reasonable yield of the fluorohydrin (IX) was obtained from the appropriate 3-cycloethylene-ketal-5α,6α-epoxide (VIII). The fluorohydrins were then converted into 6-fluoro-Δ^4-3-ketones by acid treatment as described in the sequel.

An alternate general method for the synthesis of 6-fluoro-Δ^4-3-ketones was thus available which did not require a Δ^5-3β-alcohol as a precursor. The ketal-epoxides can be prepared from the appropriate, readily available Δ^4-3-ketones by ketalization and epoxidation.

This paper describes the application of this method for the synthesis of 6α-fluorotestosterone and the 6α- and 6β-fluoro analogs of progesterone, Reichstein's Compound "S" and desoxycorticosterone acetate.

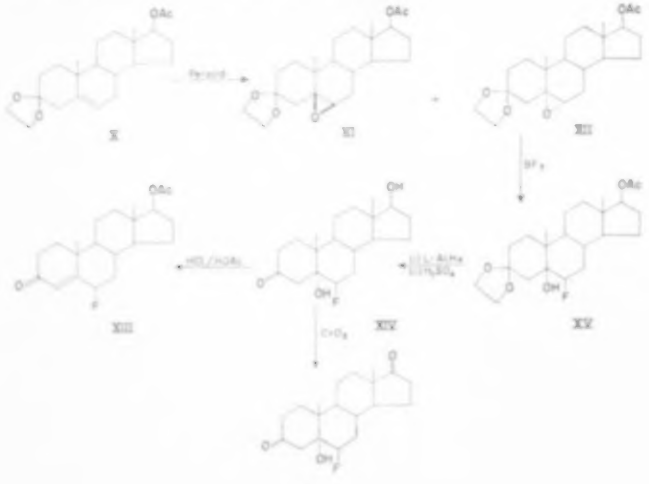

FIG. 2.

Epoxidation of testosterone acetate ketal (X)[6] (Fig. 2) with permonophthalic acid afforded a mixture of the 5β,6β-epoxide (XI) and the 5α,6α-epoxide (XII) which could be separated by chromatography over alumina. The structure proof and configurations assigned to these two epoxides followed from their mode of preparation

[5] B. Ellis and V. Petrow, *J. Chem. Soc.* 4417 (1956).
[6] R. Antonucci, S. Bernstein, R. Littel, K. J. Sax and J. H. Williams, *J. Org. Chem.* **17**, 1341 (1952).

elemental analysis, their relative polarities towards alumina and a comparison of their molecular rotations. It is known that the epoxidation of Δ^5-3β-alcohols and their esters always leads to a mixture of epoxides with the α-epoxide being predominant. Examples taken from three different series, namely the α and β-epoxides derived

TABLE 1. MOLECULAR ROTATION DIFFERENCES BETWEEN 3-CYCLOETHYLENE-KETAL-5α,6α AND 5β,6β-EPOXIDES

Compound		M_D	$\Delta M_D(\alpha - \beta)$
Testosterone acetate-3-ketal	α-Epoxide[a]	−243	−208
	β-Epoxide[a]	−35	
Progesterone-3,20-bisketal	α-Epoxide[a,b]	−209	−209
	β-Epoxide[a]	±0	
Compound S diacetate-3-mono-ketal	α-Epoxide[a]	−383	−383
	β-Epoxide[a]	±0	
Desoxicorticosterone acetate-3-mono-ketal	α-Epoxide[a]	+86	−145
	β-Epoxide[a]	+251	
21-Desoxycortisone-3,20-bisketal	α-Epoxide[c]	−177	−159
	β-Epoxide[c]	−18	
17α-Hydroxyprogesterone-3,20-bisketal	α-Epoxide[d]	−252	−196
	β-Epoxide[d]	−56	
11α-Acetoxyprogesterone-3,20-bisketal	α-Epoxide[e]	−256	−174
	β-Epoxide[e]	−82	

[a] This paper. [b] G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957). [c] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 3091 (1958). [d] J. A. Edwards and H. J. Ringold, forthcoming publication. [e] G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *J. Amer. Chem. Soc.* **78**, 6213 (1956).

from cholesterol,[7] Δ^5-androstene-17-one[8] and Δ^5-pregnene3β,21-diol-20-one diacetate,[9] show that the α-epoxide is always more polar towards alumina and has a more levorotatory specific rotation than the epimeric β-epoxide. Sufficient evidence is now available to demonstrate that these characteristic differences also apply to C-3-cycloethylene-ketal-5,6-epoxides. In Table 1 the molecular rotations of a series of epimeric 3-ketal-5,6-epoxides are collected. In every case the α-epoxide is considerably more levorotatory than the β-epimer. In addition the β-epoxides were

[7] P. A. Plattner, T. Petrzilka and W. Lang, *Helv. Chim. Acta* **27**, 513 (1944).
[8] L. Ruzicka and A. C. Muhr, *Helv. Chim. Acta* **27**, 503 (1944).
[9] L. Ruzicka, P. A. Plattner, H. Heusser and V. Ernst, *Helv. Chim. Acta* **29**, 248 (1946).

isolated from the mixture by chromatography over alumina, and in every case the β-epoxide was the less polar of the two compounds. It is possible to conclude therefore, that in any mixture of epimeric 5,6-epoxides, one can confidently define the stereochemistry of each epimer by rotation measurements and the behaviour of the mixture on chromatography over alumina.

Fission of the α-epoxide of testosterone acetate 3-cycloethylene ketal (XII) with boron trifluoride-etherate in an ether-benzene solution smoothly afforded the corresponding 6β-fluoro-5α-hydroxy-fluorohydrin (XV). Hydrolysis of the 17β-acetate group of XV with lithium aluminum hydride and mild acid hydrolysis of the ketal group led to 6β-fluoro-androstan-5α,17β-diol-3-one (XIV). Oxidation of XIV with 8 N chromic acid in acetone solution readily gave the 3,17-diketone (XVI) which was identical in every respect with an authentic specimen.[3] Treatment of XIV with anhydrous hydrogen chloride in acetic acid for 5 hr led to dehydration of the tertiary hydroxyl group at C-5, inversion of the fluorine atom from 6β to 6α[3] and acetylation of the 17β-hydroxyl group to afford in good yield 6α-fluorotestosterone acetate (XIII), identical with an authentic sample prepared by the acetylation of 6α-fluorotestosterone.[3]

Similarly 6α-fluoroprogesterone was prepared by this general method. Progesterone-bisketal[10] (XVII; Fig. 3) underwent epoxidation to give the expected mixture of α and β-epoxides.

However, in addition to the two epoxides XVIII and XIX a by-product was isolated which displayed a strong carbonyl band at 1700 cm^{-1} in the infrared which could be attributed to an unconjugated keto group at either or C-3 or C-20. Taken in conjunction with the elemental analysis this evidence indicated that the compound

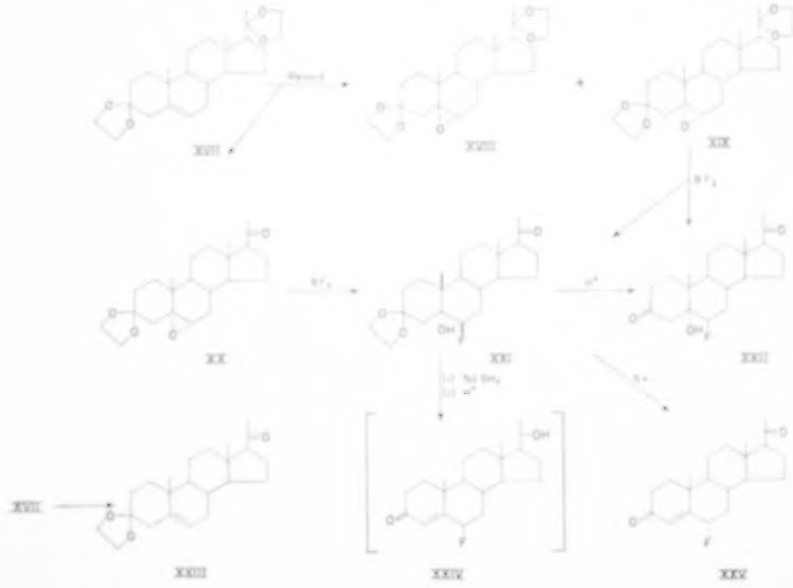

Fig. 3.

[10] R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax and J. H. Williams, *J. Org. Chem.* **17**, 1369 (1952); [3] W. S. Allen, S. Bernstein and R. Littel, *J. Amer. Chem. Soc.* **76**, 6116 (1954).

VOL. 7 1959

was a monoketal-5,6-epoxide. Presumably the acid medium of the epoxidation reaction was sufficient to partially hydrolyze one of the ketal groups. This compound could have one of four possible structures, being either a 5α,6α epoxide or a 5β,6β-epoxide with a free carbonyl group at C-3 or C-20. As will be shown in the sequel its structure was shown to be 5α,6α-oxidopregnan-3,20-dione-3-cycloethylene-ketal (XX).

Treatment of XX with boron trifluoride-etherate in benzene–ether solution led in 51 per cent yield to the fluorohydrin (XXI) which was smoothly hydrolyzed with *p*-toluenesulphonic acid and acetone to afford 6β-fluoro-5α-hydroxypregnan-3,20-dione (XXII) identical in every respect with an authentic sample.[3] Under more vigorous acid conditions, namely hydrogen-chloride in acetic acid, XXI directly afforded 6α-fluoroprogesterone (XXV).[3] These two experiments clearly demonstrated the α-configuration for the epoxide in the original monoketal-epoxide (XX)[11] but did not discriminate between the two alternate possibilities for the position of the keto group (i.e. at C-3 or C-20). To establish this point the derived fluorohydrin (XXI) was reduced with sodium borohydride and the crude product, which did not exhibit any carbonyl absorption in the infrared, was treated with anhydrous hydrogen chloride in acetic acid for 4 hr at room temperature. The resulting product (XXIV) had maximum absorption in the ultraviolet at 234–236 mμ, ε 9,970 and bands in the infrared at 1670 and 1615 cm^{-1}. This spectral data can only be interpreted on the basis of the assigned formulas for XX, XXI and XXIV.

The boron trifluoride-etherate fission of the bisketal-5α,6α-epoxide (XIX) was then studied and rather surprisingly none of the corresponding 5α-hydroxy-6β-fluoro-3,20-bisketal could be isolated. Instead we obtained two products; the major one, being formed in 46 per cent yield was the monoketal fluorohydrin (XXI) identical in every respect with the compound obtained from the boron trifluoride cleavage of the monoketal-epoxide (XX). The minor product, isolated in 9 per cent yield was the diketo-fluorohydrin (XXII). The transformation of XXII into 6β-fluoroprogesterone has been described previously.[3]

The facile selective hydrolysis of the C-20 ketal group by boron trifluoride etherate suggested a new and more convenient route for the preparation of the C-3 monoketal of progesterone (XXIII) than those described previously.[12] The bisketal of progesterone (XVII) can be obtained in high yield from progesterone[13] and when it was treated with boron trifluoride etherate in an ether–benzene solution the C-3 monoketal (XXIII), identical with an authentic sample,[12] was obtained in 82 per cent yield together with a 6 per cent yield of progesterone.

In Fig. 4 the approaches used to prepare the 6α and 6β-fluoro analogs of desoxycorticosterone acetate and Compound "S" are outlined. The starting materials were desoxycorticosterone acetate (XXVIa) and Compound "S" 17,21-diacetate (XXVIb) respectively. In each case the 3-monoketals XXVII (a and b) were prepared by the dioxolane method,[14] whence permonophthalic acid oxidation, chromatographic separation of the epimeric α- and β-epoxides (XXXI) and (XXVIII) and fission of the

[11] 3β-Acetoxy-5β,6β-epoxides are known to afford 5α-fluoro-6β-hydroxy fluorohydrins upon treatment with boron trifluoride etherate.[4]

[12] F. Sondheimer, M. Velasco and G. Rosenkranz, *J. Amer. Chem. Soc.* **77**, 192 (1955).

[13] In Ref. 10b the authors report a 79 per cent yield, but even higher yields (85–90%) have been obtained for this reaction; private communication from Dr. J. A. Zderic.

[14] H. Dauben, B. Loken and H. J. Ringold, *J. Amer. Chem. Soc.* **76**, 1359 (1954).

α-epoxides (XXXIa and b) with boron trifluoride-etherate followed the usual procedure. Treatment of the derived ketal-fluorohydrin (XXXa) in the desoxycorticosterone acetate series with hydrogen chloride in acetic acid for 4 hr smoothly led to 6α-fluorodesoxycorticosterone acetate (XXXIV). In the Compound "S" diacetate series mild hydrolysis of XXXb with *p*-toluenesulphonic acid hydrate and acetone afforded the 3-keto-fluorohydrin (XXIX). This compound gave 6α-fluoro-Compound "S" diacetate (XXXVa) after treatment for 4 hr with hydrogen chloride in acetic acid.

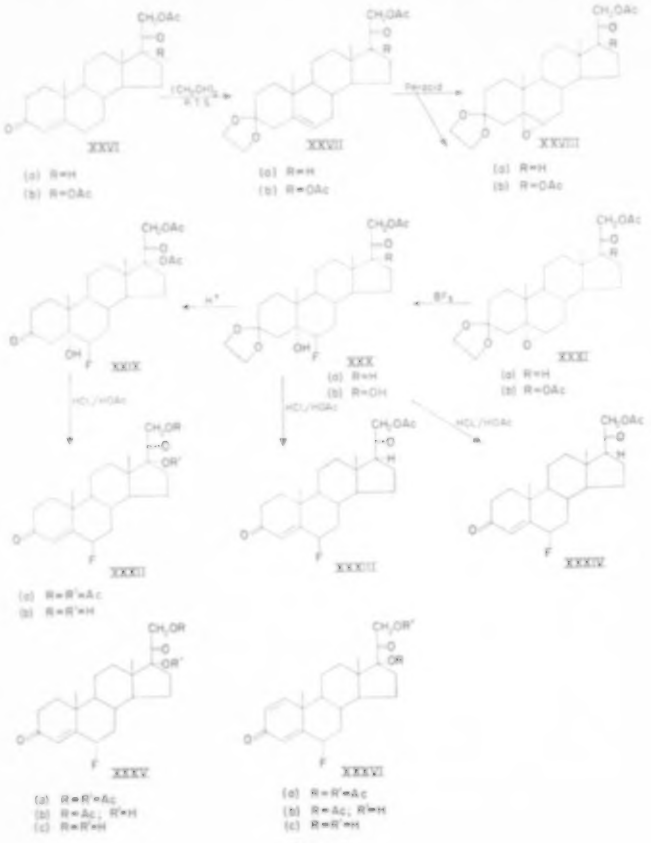

FIG. 4.

Attempts were then made to prepare 6β-fluoro-Compound "S" 17,21-diacetate (XXXIIa) by dehydration of the 3-ketofluorohydrin (XXIX) without concomitant inversion of the fluorine atom. Mild alkaline dehydration had been used successfully for the synthesis of 6β-fluoroprogesterone[3] but the instability of the dihydroxyacetone side-chain precluded its use in this series in other than low yield. However, replacement of acetic acid by anhydrous and alcohol free chloroform in the hydrogen chloride catalyzed dehydration was successful and 6β-fluoro-Compound "S" diacetate (XXXIIa) was obtained as the major product of the reaction. Unfortunately, this

[15] The lack of reproducibility in the epimerization of the 6β- to the 6α-fluoro compounds with "alcohol free" chloroform is reminiscent of the related epimerizations of 6β- to 6α-hydroxy-Δ^4-3-ketones, cf. P. T. Herzig and M. Ehrenstein, *J. Org. Chem.* **16**, 1050 (1951).

reaction was capricious and sometimes the only product isolated was the epimeric 6α-fluoro compound (XXXVa).[15] A reproducible method of preparation was developed when a careful study was made of the acetic acid-hydrogen chloride reaction. It was observed that after 25 min reaction time the product had maximum absorption at 232–234 mμ, $\varepsilon = 10{,}000$. Accordingly, if the reaction was stopped after this period 6β-fluoro-Compound "S" diacetate (XXXIIa) could be isolated in 60 per cent yield. Further treatment of XXXIIa with hydrogen-chloride in acetic acid readily converted it into the epimeric 6α-fluoro-Δ^4-3-ketone (XXXVa). Application of this method to XXXa led to 6β-fluorodesoxycorticosterone acetate (XXXIII).

VOL. 7 1959

TABLE 2. MOLECULAR ROTATION AND U.V. LIGHT ABSORPTION DIFFERENCES BETWEEN EPIMERIC 6α AND 6β-FLURO-Δ^4-3-KETONES

Compound	M_D	$\Delta M_D(6\alpha - 6\beta)$	λ_{max}	ε_{max}
6α-Fluorotestosterone[a]	+312	+312	237 mμ	14,450
6β-Fluorotestosterone[a]	±0		234 mμ	12,300
6α-Fluoro-Δ^4-androstene-3,17-dione[a]	+561	+327	235 mμ	15,490
6β-Fluoro-Δ^4-androstene-3,17-dione[a]	+234		234 mμ	12,590
6α-Fluoroprogesterone[a]	+660	+322	236 mμ	15,490
6β-Fluoroprogesterone[a]	+338		235 mμ	13,180
6α-Fluoro-Compound S 17,21-diacetate[a]	+232	+293	236 mμ	15,490
6β-Fluoro-Compound S 17,21-diacetate[a]	−61		233 mμ	11,220
6α-Fluoro-Compound S[a]	+491	+406	236 mμ	16,220
6β-Fluoro-Compound S[a]	+85		234 mμ	12,300
6α-Fluorodesoxy-corticosterone acetate[a]	+624	+285	236 mμ	15,490
6β-Fluorodesoxy-corticosterone acetate[a]	+339		234 mμ	10,230

[a] This paper.

From a study of several pairs of 6α and 6β-fluoro-Δ^4-3-ketones two characteristic differences between the C-6 epimers have emerged. The rotatory dispersion curve of a 6α-fluoro-Δ^4-3-ketone is very similar to that of the non-fluorinated parent compound,[16] whereas the 6β-fluoro-compound exhibits striking differences. At the sodium-D-line the molecular rotation difference [ΔM_D (6α-6β)] ranges from +293 to +406 (see Table 2). Secondly, although the difference in the position of maximum absorption of the two series in the ultraviolet is quite small (usually 1–3 mμ) an appreciable difference in the intensities has been observed (see Table 2). The 6α-fluoro-Δ^4-3-ketones exhibit maximum ε values from 14,450 to 16,220, whereas the

[16] C. Djerassi, J. Osiecki, R. Riniker and B. Rinker, *J. Amer. Chem. Soc.* **80**, 1216 (1958).

6β-fluoro-Δ^4-3-ketones have a much less intense maximum absorption, ranging from 10,230 to 13,180 (see Table 2).

In accordance with these characteristics 6α-fluoro-Compound "S" diacetate (XXXVa) had a rotatory dispersion curve virtually identical to that of Compound "S" diacetate and exhibited maximum ultraviolet absorption at 236 mμ, $\varepsilon = 15{,}490$, whereas 6β-fluoro-Compound "S" diacetate (XXXIIa) had a strikingly different rotatory dispersion curve and exhibited maximum absorption at 234 mμ, $\varepsilon = 11{,}220$. The 6α and 6β-fluoro analogs of desoxycorticosterone acetate (XXXIV) and (XXXIII) also had light absorption properties and rotatory dispersion curves in full accord with their assigned structures.

Mild alkaline hydrolysis of 6α-fluoro-Compound "S" diacetate (XXXVa) afforded 6α-fluoro-Compound "S" (XXXVc) characterized as the C-21-mono acetate (XXXVb). Similarly XXXIIa readily gave 6β-fluoro compound "S" (XXXIIb).

Selenium dioxide oxidation[17] of 6α-fluoro-Compound "S" diacetate (XXXVa) in tertiary butanol smoothly yielded the corresponding Δ^1-analogue (XXXVIa) which upon mild hydrolysis gave Δ^1-6α-fluoro-Compounds S (XXXVIc), characterized as the C-21 mono acetate (XXXVIb).

The syntheses of these C-6 fluoro analogs of Compound "S" and their Δ^1-derivatives made available substrates which by biochemical methods have been directly converted into 6α-fluoro-hydrocortisone and 6α-fluoroprednisolone and hence indirectly into the cortisone and prednisone analogs. These studies will form the basis of a future publication.

EXPERIMENTAL

Melting points are uncorrected. Rotations were measured in chloroform and ultraviolet absorption spectra in 95% ethanol solution. The rotatory dispersion measurements were obtained with a Rudolph Spectropolarimeter in dioxane solution using a xenon arc lamp (250–350 mμ) and a zirconium arc lamp (350–700 mμ). We are grateful to Dr. L. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin Elmer Model 21 spectrophotometer with a sodium chloride prism. The alumina used for chromatography had been suspended in boiling ethyl acetate solution for 6 hr, filtered and dried for 36 hr at 100°. The elemental analyses were carried out by Mr. J. F. Alicino Metuchen, N. Jersey and Dr. A. Bernhadt, Mulheim, Ruhr, Germany.

Boron trifluoride cleavage of 5α,6α-*oxidopregnan*-3,20-*dione* (VI)

Boron trifluoride etherate (0·5 cc) was added to a solution of 5α,6α-oxidopregnane-20-one[b] (500 mg) in benzene-ether (1 : 1; 50 cc). After keeping at room temp for 3 hr the solution was washed with 5% sodium carbonate solution and water and finally dried over sodium sulphate. Removal of the solvent afforded a product which was adsorbed from benzene (300 cc) onto alumina (30 g). Elution with benzene–ether (90 : 10; 600 cc) afforded 6β-fluoropregnan-5α-ol-3,20-dione (VII) (220 mg) m.p. 265–270°, raised by crystallization from aqueous pyridine to 276–279°, undepressed on admixture with an authentic sample.[a] The infrared spectra of the two compounds were identical.

Peracid oxidation of testosterone acetate (X)

Permonophthalic acid (3·5 g) in ether (100 cc) was added to a solution of testosterone acetate cycloethylene-ketal (X) (4·0 g) in chloroform (100 cc) at 0° over 10 min. After keeping at 0° for 16 hr the solution was washed with cold sodium carbonate solution (5%) until it was free of acid and then washed with water and finally dried over sodium sulphate. Removal of the solvent afforded a product which was adsorbed from benzene–hexane (50 : 50; 100 cc) onto neutral alumina (200 g). Elution with benzene–hexane (50 : 50; 400 cc) and benzene (400 cc) afforded after one crystallization from benzene–hexane 5β,6β-*oxidoandrostan*-17β-*ol*-3-*one*-3-*cycloethylene*-*ketal* 17-*acetate* (XI)

[17a] H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.* **21**, 239 (1956). [b] Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta* **39**, 734 (1956). [c] S. A. Szpilfogel, T. A. P. Posthumus, M. S. De Winter and D. A. Van Dorp, *Rec. Trav. Chim.* **75**, 475 (1956).

(950 mg) m.p. 141–143°, raised by crystallizations from benzene–hexane to 146–148°, $[\alpha]_D$ −9°. (Found: C, 71·02; H, 9·04; O, 20·10. $C_{23}H_{34}O_5$ requires: C, 70·74; H, 8·78; O, 20·48%).

Further elution with benzene–ether (90 : 10; 1·6 l.) gave after one crystallization from benzene–hexane *5α,6α-oxidoandrostan-17β-ol-3-one-3-cycloethylene-ketal 17-acetate* (XII) (1·5 g), m.p. 182–184°, raised by several crystallizations to 184–185°, $[\alpha]_D$ −88°. (Found: C, 70·52; H, 8·71; O, 20·41. $C_{23}H_{34}O_5$ requires: C, 70·74; H, 8·78; O, 20·48%).

6β-Fluoroandrostan-5α,17β-diol-3-cycloethylene-ketal 17-*acetate* (XV)

Boron trifluoride-etherate (0·25 cc) was added to a solution of the 5α,6α-epoxide (XII) (250 mg) in benzene–ether (1 : 1; 30 cc) and kept at 20° for 4 hr. After washing the solution with water (4 × 20 cc) and drying (Na_2SO_4), removal of the solvent gave a product which was adsorbed from benzene (20 cc) onto alumina (15 g). Elution with benzene (100 cc) afforded *6β-fluoroandrostan-5α,17β-diol-3-cycloethylene-ketal 17-acetate* (XV) (130 mg) m.p. 157–160°, raised by crystallizations from benzene–hexane to 162–164°. (Found: C, 66·19; H, 8·55; F, 4·16. $C_{23}H_{35}O_5F$. $\frac{1}{2}CH_3OH$ requires: C, 66·11; H, 8·75; F, 4·45%).

6β-Fluoroandrostan-5α,17β-diol-3-one (XIV)

The monoketal-17-acetate (XV) (400 mg) in dry ether (30 cc) was added over 5 min with stirring to a suspension of lithium aluminum hydride (300 mg) in ether (30 cc) at room temp. After stirring at room temp for a further 30 min the excess of reagent was destroyed with ethyl acetate. Isolation of the product using the saturated sodium sulphate technique[18] afforded a product which without further purification was dissolved in methanol (15 cc) containing 1 cc of aqueous sulphuric acid (8%v/v) and heated under reflux for 35 min. Addition of water and filtration afforded a crude product (230 mg) m.p. 180–185° λ_{max}^{EtOH} 232–234 mμ, ε 3,160. One crystallization from acetone–hexane afforded *6β-fluoroandrostan-5α,17β-diol-3-one* (XIV) m.p. 207–210°, λ_{max}^{EtOH} 232–234 mμ, ε 347. The analytical sample had m.p. 220–222°, $[\alpha]_D$ +15° and did not exhibit selective absorption in the ultraviolet; λ_{max}^{KBr} 1690 and 3325 cm^{-1}. (Found: C, 70·66; H, 9·00; F, 4·86. $C_{19}H_{29}O_2F$ requires: C, 70·34; H, 9·00; F, 5·85%).

6α-Fluorotestosterone acetate (XIII)

(a) 6β-Fluoroandrostan-5α,17β-diol-3-one (XIV) (150 mg) in acetic acid (10 cc) at 15–20° was treated with a steady stream of dry hydrogen chloride for 30 min and then kept at room temp for a further 5 hr. Addition of water and filtration afforded *6α-fluorotestosterone acetate* (XIII) (100 mg) m.p. 160–169°, raised by crystallizations from benzene–hexane to 176–178°, $[\alpha]_D$ +98°, λ_{max}^{EtOH} 236 mμ, ε 15,500; λ_{max}^{KBr} 1740, 1680 and 1620 cm^{-1}. (Found: C, 72·31; H, 8·68; F, 5·84. $C_{21}H_{29}O_3F$ requires: C, 72·38; H, 8·38; F, 5·45%).

(b) Acetic anhydride (0·5 cc) was added to a solution of 6α-fluorotestosterone[3] (100 mg) in pyridine (3 cc). After keeping at 20° for 17 hr addition of water and filtration afforded the 17-acetate (XIII) (85 mg) m.p. 170–176°, raised by crystallizations from acetone–hexane to 175–177°, undepressed on admixture with the product prepared as in method (a). The infrared spectra were identical.

6β-Fluoroandrostan-5α-ol-3,17-dione (XVI)

A solution of 6β-fluoroandrostane-5α,17β-diol-3-one (XIV) (100 mg) in acetone (10 cc) was oxidized with 8 N-chromic acid in the usual way.[19] After precipitation with water filtration afforded 6β-fluoroandrostane-5α-ol-3,17-dione (XVI) (80 mg) m.p. 210–215°, raised by crystallizations from acetone–hexane to 233–235°, undepressed on admixture with an authentic sample,[3] $[\alpha]_D$ +90°. The infrared spectra of the two compounds were identical.

Peracid oxidation of progesterone 3,20-*bisketal* (XVII)

Permonophthalic acid[20] (29 g) in ether (400 cc) was added over 15 min to a solution of progesterone-bisketal[10] (XVII) (30 g) (m.p. 190–192° and having no carbonyl band in the infrared) in chloroform

[18] C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, *J. Amer. Chem. Soc.* **76**, 2969 (1954).
[19a] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* **39**, (1946); [b] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *Ibid*, 2548 (1953).
[20] Prepared according to the method of E. A. Royals and L. L. Harrel, Jr., *J. Amer. Chem. Soc.* **77**, 3405 (1955).

VOL. 7 1959

(750 cc) at 0°. After keeping at 0–5° for 16 hr the solution was washed with 5% sodium carbonate solution (3 × 200 cc), water (4 × 100 cc) and dried over sodium sulphate. Removal of the solvent afforded a product which was adsorbed from benzene–hexane (50 : 50; 500 cc) onto neutral alumina (1·5 K). Elution with benzene (2 l.) afforded 5*β*,6*β*-*oxidopregnan*-3,20-*biscycloethylene-ketal* (XVIII) (8·5 g) m.p. 151–156°, raised by crystallizations from hexane to 161–163°, $[\alpha]_D$ ±0°. (Found: C, 71·42; H, 8·98; O, 19·51. $C_{25}H_{38}O_3$ requires: C, 71·74; H, 9·15; O, 19·11%).

Further elution with benzene (3 l.) and benzene–ether (90 : 10; 2·5 l.) afforded 5*α*,6*α*-oxidopregnan-3,20-biscycloethylene-ketal (XIX) 13·5 g) m.p. 154–168°, raised by three crystallizations from ethyl acetate–hexane to 178–181°, $[\alpha]_D$ −48°, (7·3 g). Further crystallizations raised the m.p. to 183–185°, $[\alpha]_D$ −50°. Lit.[21] records m.p. 186–187°, $[\alpha]_D$ −51°.

The mother liquors from the crystallizations of the bisketal-*α*-epoxide were combined and the product was rechromatographed over alumina (300 g). Elution with benzene (2·2 l.) afforded 5*α*,6*α*-oxidopregnan-20-one-3-cycloethylene ketal (XX) (3·3 g) m.p. 152–175°, raised by three crystallizations from ethyl acetate to 190–193° (1·24 g). The analytical sample had m.p. 197–199°, $[\alpha]_D$ +11°. λ_{max}^{KBr} 1695 and 1097 cm^{-1}. (Found: C, 73·68; H, 8·94; O, 17·34. $C_{23}H_{34}O_4$ requires: C, 73·76; H, 9·15; O, 17·09%).

6β-Fluoropregnan-5α-ol-20-one-3-cycloethylene-ketal (XXI)

Boron trifluoride-etherate (1·0 cc) was added to a solution of the 3-monoketal-*α*-epoxide (XX) (0·95 g) in benzene–ether (50 : 50; 100 cc). After 16 hr at room temp the solution was washed with water (4 × 50 cc), dried over sodium sulphate and evaporated to afford a residue which was adsorbed from benzene–hexane (50 : 50; 100 cc) onto alumina (100 g). Elution with benzene–hexane (50 : 50; 400 cc) afforded 6*β*-*fluoro-pregnan*-5*α*-*ol*-20-*one*-3-*cycloethylene-ketal* (XXI) (500 mg) m.p. 132–140°, raised by several crystallizations from benzene–hexane to 145–147°, $[\alpha]_D$ +38°; λ_{max}^{KBr} 3550 and 1710 cm^{-1}. (Found: C, 69·68; H, 8·93; F, 4·57. $C_{23}H_{35}O_4F$ requires: C, 70·01; H, 8·94; F, 4·82%).

The reduction and acid treatment of 6β-fluoropregnan-5α-ol-20-one-3-cycloethylene ketal (XXI)

Sodium borohydride (100 mg) in water (0·25 cc) and dioxane (2 cc) was added to a solution of the fluorohydrin-monoketal (XXI) (100 mg) in dioxane (5 cc). After 2 hr at room temp addition of water and isolation with ethyl acetate afforded a product which did not exhibit any carbonyl absorption in the infrared. The total product in acetic acid (2·0 cc) was treated with a dry stream of hydrogen chloride for 15 min and then kept at room temp for a further 3 hr. Addition of water and isolation with ether afforded a product λ_{max}^{EtOH} 234–236 mμ, ε 9970; λ_{max}^{KBr} 1670 and 1615 cm^{-1}.

6β-Fluoropregnan-5α-ol-3,20-dione (XXII)

6*β*-Fluoropregnan-5*α*-ol-20-one-3-cycloethylene-ketal (XXI) (50 mg) in acetone (5cc) containing *p*-toluenesulphonic acid hydrate (5·0 mg) was kept at 20° for 16 hr. Evaporation of the acetone and crystallization of the residue from aqueous pyridine afforded 6*β*-fluoropregnan-5*α*-ol-3,20-dione (XXII) (20 mg), m.p. 278–282°, undepressed on admixture with an authentic sample.[8] The infrared spectra of the two compounds were identical.

6α-Fluoroprogesterone (XXV)

6*β*-Fluoropregnan-5*α*-ol-20-one-3-cycloethylene-ketal (XXI) (250 mg) in acetic acid (15 cc) at 15–20° was treated with a steady stream of dry hydrogen chloride for 30 min and then kept at 20° for 4½ hr. Addition of water and isolation with ethyl acetate afforded a product which was adsorbed from benzene–hexane (50 : 50; 20 cc) onto alumina (10 g). Elution with benzene–hexane (50 : 50; 350 cc) afforded 6*α*-fluoroprogesterone (XXV) (170 mg) m.p. 90–115°, raised by crystallizations from acetone–hexane to 146–147°, (90 mg); m.p. was undepressed on admixture with an authentic sample.[8] The infrared spectra of the two samples were identical.

Boron trifluoride-etherate fission of progesterone-α-epoxide-3,20-biscycloethylene ketal (XIX)

Boron trifluoride-etherate (1·25 cc) was added to a solution of the 5*α*,6*α*-epoxide (XIX) (1·0 g) in benzene–ether (1 : 1; 100 cc) and kept at room temp for 2½ hr. After washing the solution with

[21] G. Cooley, B. E. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4112 (1957).

5% sodium carbonate solution (2 × 50 cc) and water (3 × 100 cc) and drying (Na_2SO_4) the solution was diluted with benzene (150 cc), concentrated to 100 cc and then adsorbed onto alumina (50 g). Elution with benzene (400 cc) afforded 6β-fluoropregnan-5α-ol-20-one-3-cycloethylene-ketal (XXI) (460 mg) m.p. 128–133°, raised by several crystallizations from benzene–hexane and methanol–water to 144–146° undepressed on admixture with the sample prepared as described above. The infrared spectra of the two samples were identical.

Further elution with benzene–ether (90 : 10; 250 cc) afforded after one crystallization from ethyl acetate–pyridine 6β-fluoropregnan-5α-ol-3,20-dione (XXII) (90 mg) m.p. 278–279 undepressed on admixture with an authentic specimen;[8] $[\alpha]_D$ +76° (pyridine). The infrared spectra were identical.

Boron trifluoride-etherate treatment of progesterone-biscycloethylene-ketal (XVII)

Boron trifluoride-etherate (0·5 cc) was added to a solution of progesterone biscycloethylene-ketal[10] (XVII) (500 mg) (m.p. 177–179°; $[\alpha]_D$ −29°; no carbonyl bond in the infrared) in dry benzene–ether (1 : 1; 50 cc). After 2 hr at room temp the solution was washed with 5% sodium bicarbonate solution (25 cc) and water (3 × 50 cc) and then dried (Na_2SO_4) and the solvent removed under vacuo. The product in benzene–hexane (1 : 1; 50 cc) was adsorbed onto alumina (30 g). Elution with benzene–hexane (350 cc) afforded Δ⁵-pregnen-20-one-3-cycloethylene-ketal (XXIII) (360 mg) m.p. 175–177°, raised by one crystallization from benzene–hexane to 178–180°, undepressed on admixture with an authentic sample,[12] $[\alpha]_D$ +47°; +45° (pyridine). It exhibited no selective absorption in the ultraviolet λ_{max}^{KBr} 1710 cm⁻¹ Lit[12] reports m.p. 180–181°, $[\alpha]_D$ +53° (pyridine).

Further elution with benzene (200 cc) afforded progesterone (65 mg) m.p. 114–117°, λ_{max}^{EtOH} 240–242 mμ, ε 16,200. After one crystallization from methanol–water it had m.p. 120–121°, undepressed on admixture with an authentic sample of progesterone.

Peracid oxidation of desoxycorticosterone acetate 3-monocyclo-ethylene-ketal (XXVIIa)

A solution of permonophthalic acid (53 g) in ether (800 cc) was added over 30 min to a solution of desoxycorticosterone acetate 3-monocycloethylene ketal[10a] (XXVII) (30 g) in chloroform (500 cc) at 0°. After keeping at 0° for 20 hr a further 500 cc of chloroform was added and the organic phase was washed acid free with sodium carbonate solution (5%). The solution was then washed with water (4 × 200 cc), dried (Na_2SO_4) and evaporated to afford a product which was dissolved in benzene (1 l.) and adsorbed onto neutral alumina (1 kg). Elution with benzene (5 l.) afforded after one crystallization from benzene–hexane 5β,6β-*oxido-pregnan*-21-*ol*-20-*one* 21-*acetate* 3-*cycloethylene-ketal* (XXVIIIa) (3·7 g) m.p. 195–197°, raised by crystallizations from benzene–hexane to 199–200°, $[\alpha]_D$ +58°. (Found: C, 69·52; H, 8·41; O, 22·08. $C_{25}H_{36}O_6$ requires: C, 69·42; H, 8·39; O, 22·19%).

Further elution with benzene–ether (90 : 10, 10 l.) afforded 5α,6α-*oxidopregnan*-21-*ol*-20-*one* 21-*acetate* 3-*cycloethylene-ketal* (XXXIa) (15·1 g) m.p. 238–245°, raised by several crysallizations from methanol–chloroform to 243–245°, $[\alpha]_D$ +20°. (Found: C, 69·71; H, 8·36; O, 21·81. $C_{25}H_{36}O_6$ requires: C, 69·42; H, 8·39; O, 22·19%).

6β-*Fluoropregnane*-5α,21-*diol*-20-*one* 21-*acetate* 3-*cycloethylene-ketal* (XXXa)

Boron trifluoride-etherate (4·0 cc) was added to a stirred suspension of the 5α,6α-epoxide (XXXIa) (2·0 g) in benzene–ether (1 : 1; 200 cc) at room temp. The epoxide gradually dissolved and after 6 hr the solution was washed with sodium carbonate solution (5%) and then with water. After drying (Na_2SO_4) the solvent was removed under vacuo to afford a product which was adsorbed from benzene (250 cc) onto alumina (100 g). Elution with benzene (750 cc) and benzene–ether (90 : 10; 300 cc) gave 6β-*fluoropregnan*-5α,21-*diol*-20-*one* 21-*acetate* 3-*cycloethylene-ketal* (XXXa) (930 mg) m.p. 215–218°, raised by crystallizations from benzene–hexane to 220–221°, $[\alpha]_D$ +40°. (Found: C, 66·30; H, 8·36; F, 3·95. $C_{25}H_{37}O_6F$ requires: C, 66·34; H, 8·24; F, 4·20%).

6α-*Fluoro*-Δ⁴-*pregnen*-21-*ol*-3,20-*dione* 21-*acetate* (6α-*fluorodesoxycorticosterone acetate*) (XXXIV)

Dry hydrogen chloride was passed briskly through a solution of 6β-fluoropregnan-5α,21-diol-20-one-21-acetate 3-cycloethylene-ketal (XXXa) (500 mg) in glacial acetic acid (20 cc) at 15–20° for 30 min. The solution was then kept at room temp for 4 hr. Addition of water and filtration afforded a product (360 mg) m.p. 145–156°. One crystallization from acetone–hexane yielded 6α-fluorodesoxycorticosterone acetate (XXXIV) (230 mg) m.p. 166–168°, raised by several crystallizations from

acetone–hexane to 169–171°, $[\alpha]_D$ +161°. λ_{max}^{EtOH} 236 mμ, ε 15,500. λ_{max}^{KBr} 1735, 1715, 1670 and 1625 cm⁻¹. (Found: C, 71·05; H, 7·91; F, 4·62. $C_{23}H_{31}O_4F$ requires: C, 70·73; H, 8·00; F, 4·86%).

6β-Fluoro-Δ⁴-pregnene-21-ol-3,20-dione 21-acetate (6β-fluorodesoxycorticosterone acetate (XXXIII)

Dry hydrogen chloride was passed briskly through a solution of the ketal-fluorohydrin (XXXa) (500 mg) in glacial acetic acid (25 cc) for 20 min. Addition of ice water and filtration gave a product (400 mg) m.p. 127–129° which was adsorbed from methylene dichloride (50 cc) onto a silica-celite column (50 : 50; 40 g). Elution with methylene–dichloride-benzene (50 : 50; 700 cc) afforded 6β-fluorodesoxycorticosterone acetate (200 mg) m.p. 128–132°. One crystallization from acetone-hexane gave a pure product (156 mg) m.p. 150–152°. The analytical sample had m.p. 152–154°, $[\alpha]_D$ +87°. λ_{max}^{EtOH} 234 mμ, ε 10,000 λ_{max}^{KBr} 1735, 1715, 1670 and 1625 cm⁻¹. (Found: C, 70·48; H, 8·00; F, 5·43. $C_{23}H_{31}O_4F$ requires: C, 70·73; H, 8·00; F, 4·86%).

Δ⁵-Pregnen-17α,21-diol-20-one 17,21-diacetate-3-cycloethylene-ketal (Compound "S" diacetate 3-monoketal) (XXVIIb)

A solution of Compound "S" diacetate[22] (XXVIa) (15 g) in dioxalane (300 cc) (ethylendioxy ketal of methyl ethyl ketone)[14] containing *p*-toluene-sulphonic acid (300 mg) was distilled at such a rate that 200 cc of distillate was obtained in 2½ hr. A further 200 cc of dioxalane was then added and the distillation continued for an additional 2½ hr at the same rate. The reaction mixture was then cooled, filtered and washed with a little cold methanol to afford a crude product (11·1 g) m.p. 114–117°, λ_{max}^{EtOH} 242 mμ ε 4,300. After one crystallization from methanol containing a few drops of pyridine the *monoketal* (XXVIIb) had m.p. 160–163°, λ_{max}^{EtOH} 240–242 mμ, ; 520; (6·3 g). This product was used for subsequent work. The analytical sample had m.p. 165–167°, $[\alpha]_D$ −25° and did not exhibit selective absorption in the ultraviolet. (Found: C, 68·58; H, 8·26; O, 23·02. $C_{27}H_{38}O_7$ requires: C, 68·33; H, 8·07; O, 23·60%).

Peracid oxidation of Compound "S" diacetate 3-monoketal (XXVIIb)

Permonophthalic acid (4 g) in ether (100 cc) was added over 10 min to a solution of the monoketal (XXVIIb) (3 g) in chloroform (100 cc) at −15°. After keeping at 0° for 16 hr the solution was washed with sodium bicarbonate solution (5%) until it was free of acid and then to neutrality with water. The dried solution (Na_2SO_4) was evaporated to afford a product which was adsorbed from benzene onto alumina (200 g). Elution with benzene–ether (80 : 20; 400 cc) afforded *5β,6β-oxidopregnan-17α,21-diol-20-one 17,21-diacetate 3-cycloethylene-ketal* (XXVIIIb) (630 mg) m.p. 167–169°, raised by crystallizations from ethyl acetate to 170–171°, $[\alpha]_D$ ±0°. (Found: C, 64·47; H, 7·82; O, 27·26. $C_{27}H_{38}O_8$ CH_3COOEt requires: C, 64·34; H, 8·01; O, 27·65%).

Further elution with benzene-ether (70 : 30; 600 cc) afforded after one crystallization from ethyl acetate-hexane *5α,6α-oxido-pregnan-17α,21-diol-20-one 17,21-diacetate 3-cycloethylene-ketal* (XXXIb) (780 mg) m.p. 180–182°, raised by several crystallizations from ethyl acetate to 186–188°, $[\alpha]_D$ −78°. (Found: C, 66·10; H, 7·72; O, 25·62. $C_{27}H_{38}O_8$ requires: C, 66·10; H, 7·81; O, 26·09%).

6β-Fluoropregnan-5α,17α,21-triol-20-one 17,21-diacetate 3-cycloethylene-ketal (XXXb)

Boron trifluoride-etherate (0·5 cc) was added to a solution of the α-epoxide ketal (XXXIb) (500 mg) in ether–benzene (1 : 1; 60 cc) and kept at room temp for 3½ hr. The product, isolated in the usual way, was adsorbed from benzene (50 cc) onto alumina 30 g). Elution with benzene afforded after one crystallization from benzene–hexane *6β-fluoropregnan-5α,17α,21-triol-20-one 17,21-di-acetate 3-cycloethylene-ketal* (XXXb) (250 mg) m.p. 215–219°, raised by several crystallizations from benzene–hexane to 218–219°, $[\alpha]_D$ −31°. (Found: C, 63·90; H, 7·87; F, 3·87. $C_{27}H_{39}O_8F$ requires: C, 63·51; H, 7·70; F, 3·72%).

6β-Fluoropregnan-5α,17α,21-triol-3,20-dione 17,21-diacetate (XXIX)

A solution of the monoketal-fluorohydrin (XXXb) (100 mg) in acetone (10 cc) containing *p*-toluenesulphonic acid (5 mg) was kept at room temp for 8 hr. Evaporation of the solvent and

[22] Prepared according to the method of H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78**, 820 (1956).

crystallization of the product from chloroform–methanol afforded 6β-*fluoro-pregnan*-5α,17α,21-*triol*-3,20-*dione* 17,21-*diacetate* (XXIX) (53 mg) m.p. 215–219°, raised by further crystallizations to 225–227°, $[\alpha]_D$ ±0°. (Found: C, 63·49; H, 7·73; F, 3·94. $C_{25}H_{35}O_7F$ requires: C, 63·60; H, 7·85; F, 3·74%).

6α-*Fluoro*-Δ⁴-*pregnen*-17α,21-*diol*-3,20-*dione* 17,21-*diacetate* (6α-*fluoro-Compound "S" diacetate*) (XXXVa)

Dry hydrogen chloride was bubbled for 1 hr through a solution of 6β-fluoropregnan-5α,17α,21-triol-3,20-dione 17,21-diacetate (XXIX (1·5 g) in glacial acetic acid (100 cc) at 10–15° (just above the freezing point of the solution). The flask was then stoppered and kept at room temp for a further 3 hr. Addition of water and filtration afforded 6α-*fluoro-Compound "S" diacetate* (XXXVa) (1.17 g) m.p. 225–227°, raised by crystallizations from acetone–hexane to 241–143°, $[\alpha]_D$ +53°; λ_{max} 236 mμ, ε 15,490. $\lambda_{max}^{CHCl_3}$ 1730, 1680 and 1620 cm⁻¹; XXXVa gave a positive test with triphenyltetrazolium chloride.[23]

Rotatory dispersion curve: (C, 0·061 in dioxane) $[\alpha]_{700}$ +14·8°, $[\alpha]_{589}$ +51·1°, $[\alpha]_{450}$ +87·5°, $[\alpha]_{370}$ −48°, $[\alpha]_{355}$ −64·4°, $[\alpha]_{310}$ +1850°, $[\alpha]_{295}$ +1605°.

Rotatory dispersion curve of Reichstein's Compound "S" 17,21-diacetate: (C, 0·071 in dioxane) $[\alpha]_{700}$ +21°, $[\alpha]_{589}$ +42°, $[\alpha]_{450}$ +119°, $[\alpha]_{305}$ −71·6, $[\alpha]_{355}$ −55°, $[\alpha]_{305}$ +2320°, $[\alpha]_{290}$ +1805°. (Found: C, 66·97; H, 7·70; F, 4·48. $C_{25}H_{33}O_6F$ requires: C, 66·93; H, 7·41: F, 4·24%).

6α-*Fluoro*-Δ⁴-*pregnen*-17α,21-*diol*-3,20-*dione* (6α-*fluoro-Compound "S"*) (XXXVc)

A suspension of 6α-fluoro-Compound "S" 17,21-diacetate (XXXVa) (800 mg) in methanol (8 cc) containing potassium hydroxide (80 mg) was stirred under nitrogen at 0° for 1¼ hr. After 45 min a complete solution was obtained. Acidification with acetic acid, addition of ice–salt water and filtration afforded 6α-*fluoro-Compound "S"* (XXXVc) (510 mg) m.p. 188–192, raised by several crystallizations from acetone–hexane and benzene to 203–205°, $[\alpha]_D$ +135°, λ_{max}^{EtOH} 236 mμ, ε 16,220 $\lambda_{max}^{CHCl_3}$ 3450, 1710, 1678 and 1625 cm⁻¹. (Found: C, 69·34; H, 8·34; F, 5·53. $C_{23}H_{29}O_4F$ requires: C, 69·20; H, 8·02; F, 5·21%).

The C-21 *mono acetate* (XXXVb) prepared in the usual way had m.p. 229–231° $[\alpha]_D$ +130° λ_{max}^{EtOH} 236 mμ, ε 16,100 λ_{max}^{KBr} 3470, 1745, 1720, 1660, 1620 cm⁻¹. (Found: C, 68·15; H, 7·84; F, 4·67 $C_{23}H_{31}O_5F$ requires: C, 67·99; H, 7·69; F, 4·67%).

6α-*Fluoro*-Δ¹·⁴-*pregnadien*-17α,21-*diol*-3,20-*dione* 17,21-*diacetate* (XXXVIa)

6α-Fluoro-Compound "S" diacetate (XXXVa) (2·0 g) in anhydrous tertiary butanol (100 cc) was heated under reflux with stirring under nitrogen with selenium dioxide (1·0 g) for 24 hr. Ethyl acetate (100 cc) was then added and the solution filtered through celite to remove the precipitated selenium. Evaporation of the solvent afforded a product which was slurried with water (200 cc) filtered, dried and crystallized from acetone–hexane to afford 6α-*fluoro*-Δ¹·⁴-*pregnadien*-17α,21-*diol*-3,20-*dione* 17,21-*diacetate* (XXXVIa) (1·11 g) m.p. 246–248; raised by crystallizations from acetone–hexane to 251–253° $[\alpha]_D$ ±0. λ_{max} 242 mμ, ε 16,950. (Found: C, 67·03; H, 7·09; F, 4·69. $C_{25}H_{31}O_6F$ requires: C, 67·23; H, 7·00; F, 4·26%).

6α-*Fluoro*-Δ¹·⁴-*pregnadien*-17α,21-*diol*-3,20-*dione* (XXXVIc)

A suspension of 6α-fluoro-Δ¹·⁴-pregnadiene-17α,21-diol-3,20-dione 17,21-diacetate (XXXVIa) (1·0 g) in methanol (10 cc) containing potassium hydroxide (100 mg) was stirred under nitrogen at 0° for 1 hr. After 35 min a complete solution was obtained. Acidification with acetic acid, addition of ice–salt water and filtration afforded 6α-fluoro-Δ¹·⁴-pregnadien-17α,21-diol-3,20-dione (XXXVIc) (740 mg) m.p. 209–214°, raised by several crystallizations from ethyl acetate–hexane to 210–212°, $[\alpha]_D$ +66°; λ_{max}^{EtOH} 240–242 mμ, ε 16,600. (Found: C, 69·40; H, 7·74; F, 5·06. $C_{21}H_{27}O_4F$ requires: C, 69·60; H, 7·51; F, 5·24%).

The C-21-*mono acetate* (XXXVIb) prepared in the usual way (pyridine–acetic anhydride) had m.p. 224–224°, $[\alpha]_D$ +104°; λ_{max} 240 mμ, ε 16,000. (Found: C, 68·76; H, 7·55; F, 4·83. $C_{23}H_{29}O_5F$ requires: C, 68·31; H, 7·23; F, 4·70%).

[23] R. B. Burton, A. Zaffaroni and H. E. Keutmann, *J. Biol. Chem.* **188**, 763 (1951).

VOL. 7 1959

6β-Fluoro-Δ⁴-pregnen-17α,21-diol-3,20-dione 17,21-diacetate (6β-fluoro-Compound "S" diacetate) (XXXIIa)

(a) Dry hydrogen chloride was bubbled for 3 hr through a suspension of 6β-fluoro-pregnan-5α,17α,21-triol-3,20-dione 17,21-diacetate (XXIX) (500 mg) in anhydrous and alcohol free chloroform[21] (50 cc) at 0–5°. The flask was then stoppered and kept for 16 hr at room temp with occasional shaking. During this period the steroid gradually dissolved in the solution. Addition of water and isolation with chloroform afforded 6β-fluoro-Compound "S" diacetate (XXXIIa) (409 mg), λ_{max} 234–236 mμ, ε 9,750, m.p. 175–183° raised by several crystallizations from acetone–hexane to 187–189°, $[\alpha]_D$ −14°, λ_{max} 234 mμ, ε 11,220.

Rotatory dispersion curves: (C, 0·072 in dioxane) $[\alpha]_{700}$ −48·6° $[\alpha]_{589}$ −41°, $[\alpha]_{579}$ −352°, $[\alpha]_{565}$ −377°, $[\alpha]_{315}$ +1340° $[\alpha]_{300}$ +1215°. (Found: C, 66·53; H, 7·36; F, 4·42. $C_{25}H_{32}O_6F$ requires: C, 66·93; H, 7·41; F, 4·24%).

This experiment was not reproducible,[15] from 5 experiments the 6β-fluoro-compound (XXXIIa) was isolated twice and in the other three experiments only the 6α-fluoro compound (XXXVa) could be isolated.

(b) Dry hydrogen chloride was bubbled for 15 min through a solution of 6β-fluoropregnan-5α,17α,21-triol-3,20-dione 17,21-diacetate (XXIX) (1·0 g) in glacial acetic acid (100 cc) at 15°. The stoppered flask was then kept at room temp for 10 min when addition of water and filtration afforded 6β-fluoro-Compound "S" diacetate (XXXIIa) (750 mg) m.p. 170–175°, raised by chromatography over neutral alumina to 185–187°, (510 mg). This product was identical with the compound prepared by method (a).

6β-Fluoro-Δ⁴-pregnene-17α,21-diol-3,20-dilne (6β-fluoro-Compound "S") (XXXIIb)

A suspension of 6β-fluoro-Compound "S" 17,21-diacetate (XXXIIa) (1·2 g) in methanol (12 cc) containing potassium hydroxide (120 mg) was stirred under nitrogen at 0° for 1½ hr. After 1 hr a complete solution was obtained. Acidification with acetic acid, addition of ice–salt water and filtration afforded 6β-fluoro-Compound "S" (XXXIIb) (800 mg) m.p. 215–218°, raised by crystallizations from acetone–hexane to 222–224°, $[\alpha]_D$ +25°. (Found: C, 69·18; H, 8·22; F, 4·95. $C_{21}H_{29}O_4F$ requires: C, 69·20; H, 8·02; F, 5·21%).

[21] Obtained by washing commercial chloroform several times with concentrated sulphuric acid and then water and finally distilling from calcium chloride.

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VOL.
7
1959

STEROIDS—CXXI[1] SYNTHESIS OF HALOGENATED STEROID HORMONES

6α-FLUORO CORTICAL HORMONES A NEW CLASS OF POWERFUL CORTICOIDS[2]

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Abstract—Incubation of 6α-fluoro Reichstein's Compound "S" (I) and its Δ^1-analog (IV) with bovine adrenals followed by acetylation led to 6α-fluorohydrocortisone acetate (II) and 6α-fluoroprednisolone acetate (III) respectively. Selenium dioxide oxidation of II also afforded III. Chromium trioxide oxidation of II and III gave 6α-fluorocortisone acetate (VIIa) and 6α-fluoroprednisone acetate (VIIIa) respectively. An alternate, all-chemical synthesis of 6α-fluorocortisone acetate (VIIa) from cortisone acetate (V) is described.

Dehydration of 6α-fluorohydrocortisone acetate gave 6α-fluoro-$\Delta^{9(11)}$-dehydro-Compound "S" (XIV). Formation of the corresponding 9β,11β-epoxide (XV) and reaction with hydrogen fluoride then gave 6α,9α-difluorohydrocortisone acetate (XVI) which afforded the prednisolone analog (XVII) upon oxidation with selenium dioxide.

IN 1954 Fried and Sabo[3] reported the synthesis of the first fluorinated steroid hormone, 9α-fluorohydrocortisone. This compound was remarkable in that it exhibited approximately ten times the liver glycogen activity of hydrocortisone in the adrenalectomized rat and approximately twenty times the glucocorticoid activity of hydrocortisone in man.[4] In addition it had mineralocorticoid activity equal to that of aldosterone.[4]

These findings stimulated a considerable interest in fluorinated steroid hormones which was increased when some 12α-fluoro-[5] and 21-fluoro steroid hormones[6] were shown to exhibit more favorable biological activities as compared to the non-fluorinated parent compounds.

In view of these remarkable biological findings it seemed desirable to investigate the synthesis of steroid cortical hormone analogs with fluorine substituents in positions other than C-9, C-12 and C-21.

Recently we described the synthesis of several 6α- and 6β-fluoro steroid hormones[1,7] and in this paper we wish to report an extension of this work to the synthesis of a series of 6α-fluoro-[2] and 6α,9α-difluoro-cortical hormones. These compounds represent a new class of highly active cortical hormones.

[1] Part CXX: A. Bowers, L. C. Ibáñez and H. J. Ringold, *Tetrahedron* **7**, 138 (1959).
[2] A preliminary announcement of part of this work has been published: A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **80**, 4423 (1958). This work was also presented in part by A. B. at the Steroids and Natural Products Section of the Gordon Research Conference, August 1958.
[3] J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **76**, 1455 (1954); *Ibid.* **79**, 1130 (1957).
[4] For a full discussion of the biological and clinical effects of a 9α-fluorine atom cf. J. Fried and A. Borman, *Vitamins and Hormones* **16**, 303 (1958).
[5a] J. E. Herz, J. Fried and E. F. Sabo, *J. Amer. Chem. Soc.* **78**, 2017 (1956); [5b] D. Taub, R. D. Hoffsommer and N. L. Wendler, *Ibid.* **78**, 2912 (1956).
[6a] P. Tannhauser, R. J. Pratt and E. V. Jensen, *J. Amer. Chem. Soc.* **78**, 2658 (1956); [6b] J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, *Ibid* **78**, 4812 (1956).
[7] A. Bowers and H. J. Ringold, *Tetrahedron* **3**, 14 (1958).

10A—(4 pp.)

In view of the availability of 6α-fluoro Reichstein's Compound "S" (6α-fluoro-Δ^4-pregnen-17α,21-diol-3,20-dione)[1] (I) and the reported transformation of Compound "S" into hydrocortisone by biochemical methods,[8,9] a plausible route to 6α-fluorohydrocortisone appeared to be by 11β-hydroxylation of 6α-fluoro-Compound "S" (I). It was considered unlikely that the fluorine atom at C-6 would interfere markedly with enzymatic hydroxylation at C-11.

Indeed, incubation of 6α-fluoro-Compound "S" (I) with bovine adrenals[9,10] from freshly killed animals led in 65 per cent yield to 6α-fluorohydrocortisone, isolated as the C-21-monoacetate (II).[11] These two conversions are the first instances of adrenal incubation of compounds containing halogen substituents.

Selenium dioxide[12] oxidation of II smoothly afforded 6α-fluoroprednisolone acetate (III). The latter compound was also prepared by the adrenal incubation of Δ^1-dehydro-6α-fluoro-Compound "S"[1] (IV) followed by acetylation.

A rigorous proof that compounds II and III have the assigned structures is presented in the sequel.

6α-Fluorocortisone acetate (Va) and 6α-fluoroprednisone acetate (VIa) were then obtained by the respective oxidations of II and III with 8 N chromic acid in acetone solution.[13]

An alternate, completely chemical route to 6α-fluorocortisone acetate was then investigated. Previous work[1] has shown that 6-fluoro-Δ^4-3-ketones can be prepared from the parent Δ^4-3-ketones by boron trifluoride etherate cleavage of their derived 3-cycloethylene ketal 5α,6α-epoxides followed by treatment with anhydrous hydrogen chloride.

However in view of the known instability of 17α-hydroxy-20-ketones (with or without a C-21-hydroxyl group) to some types of Lewis acids, for example, aluminum isopropoxide[14a,b] or boron trifluoride in acetic acid[14b,15a–c] readily induce D-homo rearrangement, it was necessary to establish the stability of this ketol system to an excess of boron trifluoride in an ether–benzene mixture for 3 hr at room

[8] Several groups have utilized an 11β-hydroxylating micro-organism, cf. [a] D. R. Collingsworth, M. P. Brunner and W. J. Haines, *J. Amer. Chem. Soc.* **74**, 2381 (1952); [b] P. W. O'Connel, K. M. Mann, E. D. Neilson and F. R. Hanson, *J. Appl. Microbiol.* **3**, 16 (1955); [c] G. M. Shull and D. A. Kita, *J. Amer. Chem. Soc.* **77**, 763 (1955).

[9] An alternative approach to 11β-hydroxylation has been via incubation with bovine adrenals: A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas and C. Djerassi, *J. Amer. Chem. Soc.* **80**, 6110 (1958).

[10] The formation of 6α-chlorohydrocortisone by the adrenal incubation of 6α-chloro-Compound "S" has been reported recently, cf. H. J. Ringold, O. Mancero, C. Djerassi, A. Bowers, E. Batres, H. Martinez, E. Necoechea, J. Edwards, M. Velasco, C. C. Campillo and R. I. Dorfman, *J. Amer. Chem. Soc.* **80**, 6464 (1958).

[11] Simultaneous with our earlier communication[2] a preliminary announcement from the Upjohn Laboratories reported the synthesis of a series of 6α-fluoro- and 6α,9α-difluorocortical hormones by an independent method; J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chem. & Ind.* 1002 (1958).

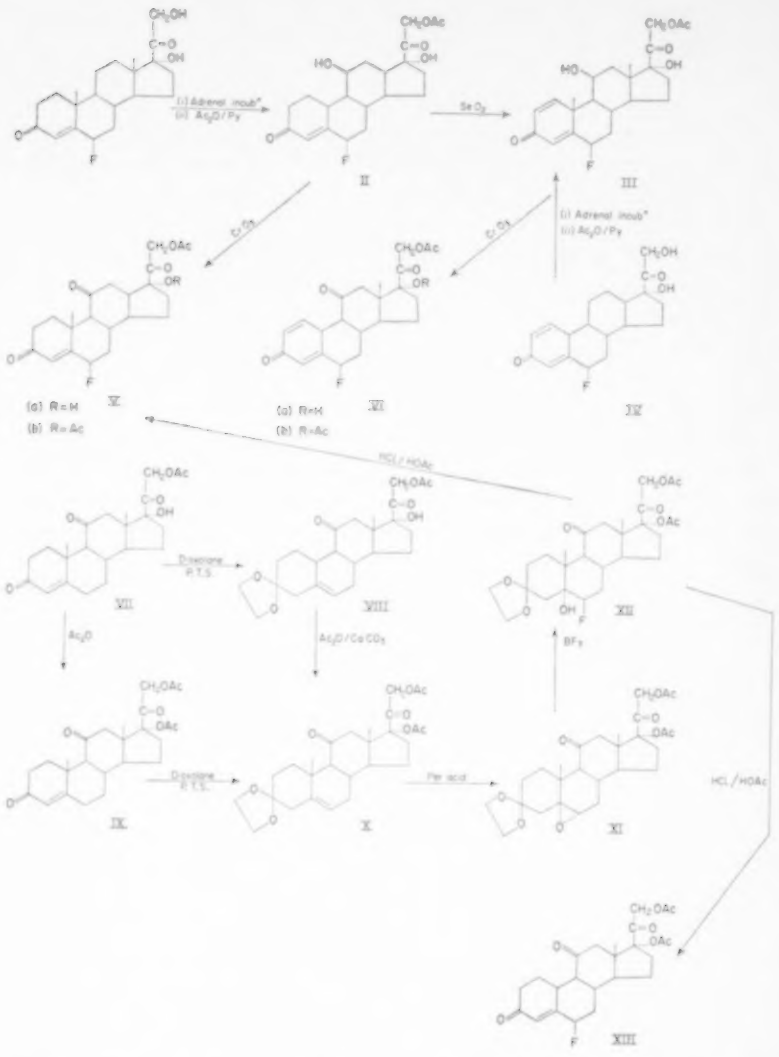
[12a] H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.* **21**, 239 (1956); [b] Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta* **39**, 734 (1956); [c] S. A. Szpilfogel, T. A. P. Posthumus, M. S. De Winter and D. A. van Dorp, *Rec. Trav. Chim.* **75**, 457 (1956); [d] K. Florey and A. R. Restivo, *J. Org. Chem.* **22**, 406 (1957).

[13a] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* **39**, (1946); [b] A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *Ibid.* 2548 (1953).

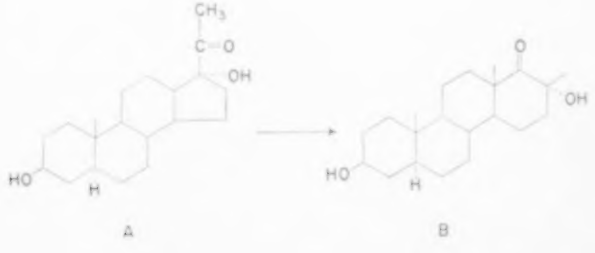
[14a] H. E. Stavely, *J. Amer. Chem. Soc.* **63**, 3127 (1941); [b] D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling and G. Roberts, *Ibid.* **77**, 6585 (1955).

[15a] C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta* **26**, 201 (1943); [b] N. L. Wendler and D. Taub, *Chem. & Ind.* 505 (1955); [c] N. L. Wendler, D. Taub, D. K. Fukushima and S. Dobriner, *Ibid.* 1259 (1955).

VOL. 7 1959



temperature. Although these conditions are much milder than any reported previously[14,15] D-homo rearrangement does occur.



Compound L (allopregnane-3β,17α-diol-20-one) (A) for example, afforded 3β,17α-dihydroxy-17β-methyl-D-homoandrostane-17a-one (B)[14b] in 51 per cent yield, together with a by-product m.p. 196–197°, $[\alpha]_D$ + 118° in 16 per cent yield. The by-product exhibited bands in the infrared at 339 cm^{-1}, 1700 cm^{-1} and 1683 cm^{-1}.

However, 17α-acetoxy-20-ketones are known to be stable to Lewis acids.[16] Thus a desirable precursor for the preparation of 6α-fluorocortisone acetate appeared to be the ketal-epoxide diacetate (XI) and two alternate routes to XI from cortisone acetate (VII) were investigated.

The room temperature acetylation of cortisone acetate with acetic anhydride and acetic acid in the presence of *p*-toluene-sulfonic acid is known to afford cortisone diacetate[16a,17] but we were not able to obtain better than a 38 per cent yield of the diacetate (IX) by this method. A similar yield was obtained by acetylating cortisone acetate with acetic anhydride under reflux for 24 hr in a nitrogen atmosphere.[18] However ketalization of IX by the dioxolane method[19] did lead to the corresponding 3-cycloethylene ketal (X), albeit in only 53 per cent yield. A superior approach to X was then developed via cortisone acetate-3-cycloethylene ketal (VIII).[20] This compound has been prepared from cortisone acetate (VII) in 94 per cent yield[20b,21] by the dioxolane method[19] and it remained only to acetylate at C-17 with preservation of the acid labile ketal system. This was carried out by heating a solution of the ketal monoacetate (VIII) in acetic anhydride under reflux for 24 hr in a nitrogen atmosphere in the presence of finely divided calcium carbonate. Under these conditions a 55 per cent yield of the ketal diacetate (X) was obtained. Epoxidation of X with monoperphthalic acid then led in high yield to the α-epoxide (XI), which underwent fission with boron trifluoride[1,7,22] in anhydrous benzene–ether solution to afford the 6β-fluoro-5α-hydroxy fluorohydrin (XII). Anhydrous hydrogen chloride treatment of XII for 25 min[1] gave 6β-fluorocortisone diacetate (XIII). Prolongation of the reaction time to 24 hr afforded 6α-fluorocortisone diacetate (Vb). The molecular rotations and ultraviolet light absorption properties of XIII and Vb were in full accord with their assigned structures.[23] It is noteworthy that the time for complete inversion of the 6β-fluorine atom in the presence of the 11-keto group is greater than that of an 11-desoxy-6β-fluoro-Δ^4-3-ketone.[24]

Selenium dioxide oxidation[12] of 6α-fluorocortisone diacetate (Vb) smoothly afforded 6α-fluoroprednisone diacetate (VIb). Mild alkaline hydrolysis of Vb in a nitrogen atmosphere followed by room temperature acetylation with acetic anhydride and pyridine led to 6α-fluorocortisone acetate (Va) identical in every respect with the product obtained by the chromic acid oxidation of 6α-fluorohydrocortisone acetate

[16a] R. B. Turner, *J. Amer. Chem. Soc.* **75**, 3489 (1953); [b] H. J. Ringold, B. Loken, G. Rosenkranz and F. Sondheimer, *Ibid.* **78**, 816 (1956).

[17] In the absence of acetic acid the major product from this reaction is $\Delta^{3,5}$-pregnadiene-3,17α,21-triol-11,20-dione triacetate, cf. A. Bowers, L. C. Ibáñez and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 3707 (1959).

[18] Huang-Minlon, E. Wilson, N. L. Wendler and M. Tishler, *J. Amer. Chem. Soc.* **74**, 5394 (1952).

[19] H. Dauben, B. Loken and H. J. Ringold, *J. Amer. Chem. Soc.* **76**, 1359 (1954).

[20a] R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.* **18**, 70 (1953); [b] F. Sondheimer, O. Mancera and G. Rosenkranz, *J. Amer. Chem. Soc.* **76**, 5020 (1954).

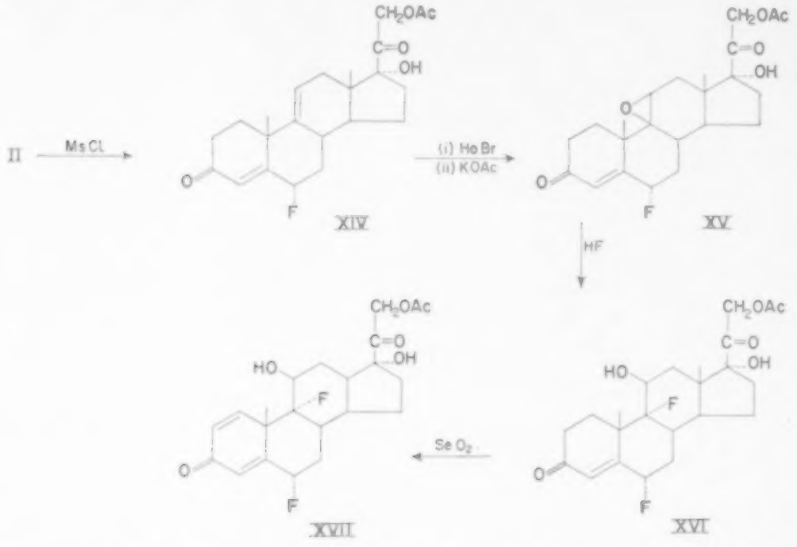
[21] The excellent yield in this reaction may be due to the highly insoluble nature of VIII, the ketal precipitating as the reaction proceeds. The ketal diacetate (X), however, is soluble in the reaction mixture and it could only be isolated in 53% yield from IX.

[22] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4765 (1957).

[23] For a discussion of the characteristic differences of the ultraviolet light absorption spectra and molecular rotations between epimeric C-6-fluoro-Δ^4-3-ketones.[1]

[24] The reported epimerizations of 6β-fluoroprogesterone[7] and 6β-fluoro-Compound "S" diacetate.[1]

(II). This reaction sequence affords unambiguous proof that the adrenal incubation of both I and IV introduced a C-11 hydroxyl group. The 11β-stereochemistry of the hydroxyl group follows from its method of introduction[25] and its inertness to acetylation with acetic anhydride and pyridine[26] (see Experimental section).



In view of the known effect of a 9α-fluorine atom on biological activity[3,4] it was of considerable interest to prepare 6α,9α-difluorohydrocortisone acetate (XVI) and its Δ^1-analog (XVII). The introduction of the 9α-fluorine atom into 6α-fluorohydrocortisone (II) was carried out using essentially the method of Fried and Sabo.[3] Treatment of II with methane sulfonyl chloride in pyridine-dimethyl formamide at 80° for 2 hr[27] led in good yield to 6α-fluoro-$\Delta^{9(11)}$-Compound "S" (XIV). Conversion of XIV to the 9β,11β-epoxide (XV) followed the usual procedure of treatment with hypobromous acid to afford the 9α-bromo-11β-hydroxybromohydrin which without purification was cylized to the β-epoxide (XV) with potassium acetate in acetone. Finally, rupture of the epoxide with hydrogen fluoride by the Merck modification[28] of Fried and Sabo's original method[3] gave 6α,9α-difluorohydrocortisone acetate (XVI). Selenium dioxide[14] oxidation of XVI afforded 6α,9α-difluoroprednisolone (XVII).

Biological activities

As can be seen from Table 1, the introduction of a 6α-fluorine atom increases anti-inflammatory and thymolytic activities by a factor of from five to ten.[29] VIIa exhibited neither sodium retention nor sodium excretion properties while compounds

[25] Adrenal incubation of all ring C desoxy steroids reported to date has always resulted in 11β-hydroxylation.[9,10]

[26] 11α-Hydroxy Compound "S" (epi-hydrocortisone) is readily acetylated at C-11 under these conditions; cf. [6] J. Romo, A. Zaffaroni, J. Hendrichs, G. Rosenkranz, C. Djerassi and F. Sondheimer, *Chem. & Ind.* 783 (1952); [5] J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 1277 (1953).

[27] J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *J. Amer. Chem. Soc.* **77**, 4181 (1955). We are very grateful to Dr. J. Fried for supplying us with the details of this method prior to publication.

[28] R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, *J. Amer. Chem. Soc.* **78**, 4956 (1956).

II, III and VIIIa were sodium excretors.[29] In contrast to the very high sodium retaining properties of 9α-fluorohydrocortisone acetate[3] and 9α-fluoroprednisolone acetate[30] the corresponding 6α-fluoro analogs XVI and XVII were only mild sodium retainers.[29]

TABLE 1. BIOLOGICAL ACTIVITIES OF 6α-FLUORO AND 6α,9α-DIFLUORO CORTICOIDS

Compound	Anti-inflammatory activity[a]	Thymolytic activity[a]
6α-Fluorocortisone acetate (VIIa)	10	6
6α-Fluorohydrocortisone acetate (II)	10	8
6α-Fluoroprednisone acetate (VIIIa)	20	23
6α-Fluoroprednisolone acetate (III)	20	62
6α,9α-Difluorohydrocortisone acetate (XVI)	50	100
6α,9α-Difluoroprednisolone acetate (XVII)	200	200

[a] Anti-inflammatory (cotton pellet implant) and thymolytic activities in immature adrenalectomized rats, oral route, hydrocortisone acetate = 1.

EXPERIMENTAL

For general directions see the preceding paper.

Boron trifluoride-etherate treatment of compound L

Boron trifluoride-etherate (1·0 cc) was added to a suspension of compound L (allopregnane-3β,17α-diol-20-one) (1·0 g) in dry benzene (100 cc) and ether (100 cc) at room temp. After 3 hr at room temp. (complete solution after 15 min) the solution was washed with water to neutrality, dried, evaporated to 50 cc and then adsorbed onto neutral alumina. Elution with benzene–ether (95 : 5; 400 cc) afforded a product (160 mg) m.p. 193–196°, raised by several crystallizations from acetone to 196–197°, $[\alpha]_D$ +120°. It exhibited no selective absorption in the ultraviolet. λ_{max}^{KBr} 3390, 1700 and 1685 cm.$^{-1}$. (Found: C, 78·70; H, 10·40%).

Further elution with benzene–ether (80 : 20; 900 cc) afforded 3β,17α-dihydroxy-17β-methyl-D-homoandrostane-17a-one (510 mg) m.p. 172–176°, raised by several crystallizations to 181–182°, $[\alpha]_D$ +28°. Lit[16] reports m.p. 182–182·5°. $[\alpha]_D$ +32·9°.

6α-Fluorohydrocortisone acetate (II)

The following solutions were used for the incubation medium:

(a) *Saline solution.* A mixture of: 200 cc of 4·5% sodium chloride, 8 cc of 5·75% potassium chloride and 2 cc of 19·1% magnesium sulfate was diluted to 1 l.

[29] The biological assays were carried out by Dr. R. I. Dorfman, at the Worcester Foundation for Experimental Biology and Endocrine Laboratories, Madison, Wisconsin. The salt assays were carried out in adrenalectomized rats without sodium load, subcutaneous route.

[30a] R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *J. Amer. Chem. Soc.* 77, 3166 (1955); [b] J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *Ibid.* 77, 4181 (1955).

(b) *Buffer solution.* (Phosphate buffer solution, 0·1 M, pH 7·4). Consists of a mixture of 850 cc of 0·1 M K_2HPO_4 (17·42 g/l.) and 150 cc of 0·1 M NaH_2PO_4 (13·8 g/l.).

(c) *Sodium fumarate solution.* Fumaric acid (17·4 g) and sodium hydroxide (12·0 g) were dissolved in water (approx 500 cc) and the pH of the mixture was adjusted to 7·0 with a potentiometer by the addition of small amounts of fumaric acid or sodium hydroxide. The solution was then diluted to 1000 cc with distilled water.

The incubation medium was made by mixing 1000 cc of solution (a), 110 cc of solution (b) and 270 cc of solution (c). For the incubation there were used 2 parts of medium for 1 part of glands.

Procedure. The bovine adrenal glands were obtained from the slaughter house just before use and kept in ice during the time of transportation to the laboratory, covered with 1% sodium chloride solution. The superficial fat was removed prior to use.

Five kilograms of the clean glands were ground in a meat grinder and suspended in 10 l. of the aforementioned incubation medium. 6α-Fluoro-Compound "S" (I) (5 g) in propylene glycol (40 cc) was then added and the mixture was stirred for 3 hr at 22°. Acetone (30 l.) was then added and the suspension stirred for 2 hr and filtered. The residue was extracted with a further 5 l. of hot acetone and the combined filtrates were concentrated *in vacuo* at 30–35° until the distillate was almost free of acetone. The residual solution was then extracted with hexane (5 l.) to remove fat and then with methylene dichloride (40 l.) (10 × 4 l.). The methylene dichloride was removed at 30° *in vacuo* and the residue was dissolved in pyridine (50 cc) containing acetic anhydride (5·0 cc) and kept at room temp for 18 hr (alternatively it was heated at 95° for 45 min). Addition of ice water afforded a product which was extracted with ethyl acetate. The ethyl acetate solution was washed with water, 2 N HCl, 5% sodium bicarbonate solution and finally water. After drying (Na_2SO_4) and removal of the solvent *in vacuo* the residue was crystallized from acetone–hexane to afford *6α-fluorohydrocortisone acetate* (II) (3·3 g), m.p. 209–211°, raised by several crystallizations from acetone–hexane to 215–217°, $[\alpha]_D$ +153° (dioxane), λ_{max}^{EtOH} 236–238 mμ, ε 16,600, λ_{max}^{KBr} 3500, 1750, 1725, 1660, 1600 (sh.) cm.$^{-1}$. R.D. (*c*, 0·0565): $[\alpha]_{700}$ +111°, $[\alpha]_{589}$ +149°, $[\alpha]_{390}$ +384°, $[\alpha]_{370}$ +318°, $[\alpha]_{357\cdot5}$ +444°, $[\alpha]_{355}$ +418°, $[\alpha]_{317\cdot5}$ +2860°, $[\alpha]_{300}$ +1280°. (Found: C, 65·30; H, 7·61; F, 4·79. $C_{23}H_{31}O_6F$ requires: C, 65·04; H, 7·47; F, 4·54%).

6α-Fluoroprednisolone acetate (*6α-fluoro-Δ^{1,4}-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate*) (III)

(a) *By the selenium dioxide oxidation of* II. Selenium dioxide (150 mg) was added to a solution of 6α-fluorohydrocortisone acetate (II) (300 mg) in t-butyl alcohol (30 cc) containing pyridine (0·04 cc) and heated under reflux with stirring in a nitrogen atmosphere for 24 hr. Ethyl acetate (30 cc) was added and the solution filtered through celite. After removal of the solvent the residue was triturated with water (50 cc), filtered, dried and adsorbed from benzene (100 cc) onto alumina (25 g). Elution with benzene–ether (50 : 50; 375 cc) afforded *6α-fluoroprednisolone acetate* (III) (157 mg), m.p. 235–240°, raised by several crystallizations from ethyl acetate–hexane to 237–239°, $[\alpha]_D$ +114° (dioxane), λ_{max}^{EtOH} 242 mμ, ε 17,750, λ_{max}^{KBr} 3450, 1755, 1730, 1677, 1620 and 1608 cm.$^{-1}$. R.D. (*c*, 0·0642): $[\alpha]_{700}$ +84·1°, $[\alpha]_{589}$ +106°, $[\alpha]_{317\cdot5}$ +3170°, $[\alpha]_{300}$ +1380°, $[\alpha]_{285}$ −836°. (Found: C, 65·34; H, 7·04; F, 4·50. $C_{23}H_{29}O_6F$ requires: C, 65·36; H, 7·02; F, 4·56%).

(b) *By the adrenal incubation of* Δ^1-*6α-fluoro-Compound "S"* (IV). Using the same technique as described above for the preparation of 6α-fluorohydrocortisone acetate (I → II) adrenal incubation of Δ^1-6α-fluoro-Compound "S" (3·0 g) afforded after acetylation and crystallization from ethyl acetate–hexane *6α-fluoroprednisolone acetate* (III) (1·23 g), m.p. 229–234°, raised by crystallizations from ethyl acetate–hexane to 236–238°, undepressed on admixture with a sample prepared by method (a). The infrared spectra were identical.

6α-Fluorocortisone acetate (Va)

6α-Fluorohydrocortisone acetate (II) (150 mg) in acetone (7·0 cc) at 0° was treated with a slight excess of 8 N chromic acid[13] (permanent orange color) and then kept at 0–5° for 2 min. Addition of water and filtration afforded *6α-fluorocortisone acetate* (Va) (140 mg), m.p. 215–220°, raised by crystallizations from acetone–hexane to 222–223°, $[\alpha]_D$ +190°, λ_{max} 233 mμ, ε 16,220. (Found: C, 65·05; H, 7·20; F, 4·97. $C_{23}H_{29}O_6F$ requires: C, 65·36; H, 7·02; F, 4·56%).

6α-Fluoroprednisone acetate (VIa)

6α-Fluoroprednisolone acetate (III) (61 mg) in acetone (6 cc) at 0° was treated with a slight excess of 8 N chromic acid[13] (permanent orange color) and then kept at 0–5° for 2 min. Addition of water

and filtration afforded 6α-*fluoroprednisone acetate* (VIa) (52 mg), m.p. 223–225° raised by crystallizations from acetone–hexane to 224–226°, $[\alpha]_D$ +142° (dioxane), λ_{max} 238 mμ, ε 15,500. (Found: C, 65·39; H, 6·61; F, 4·40. $C_{23}H_{27}O_6F$ requires: C, 65·67; H, 6·57; F, 4·59%).

Cortisone diacetate (Δ⁴-*pregnene*-17α,21-diol-3,11,20-*trione* 17,21-*diacetate*) (IX)

(a) Cortisone acetate (VII) (5·0 g) dissolved in acetic acid (225 cc) and acetic anhydride (33·7 cc) containing *p*-toluenesulfonic acid monohydrate (4·5 g) was kept at 20° during 16 hr. Addition of ice water and filtration afforded a product which was adsorbed from benzene onto alumina (300 g). Elution with benzene–ether (90 : 10; 400 cc) and one crystallization from methanol gave cortisone diacetate (IX) (1·97 g), m.p. 223–225°, $[\alpha]_D$ +140°, λ_{max}^{EtOH} 238 mμ, ε 16,600. Lit[35] reports m.p. 221–222°, $[\alpha]_D$ +133°.

(b) Cortisone acetate (10 g) in acetic anhydride (200 cc) was heated under reflux in an atmosphere of nitrogen for 24 hr. The solution was then concentrated to 50 cc *in vacuo* and the product precipitated by addition of ice water (500 cc). Crystallization from methanol afforded cortisone diacetate (IX) (4.3 g) m.p. 221–223° undepressed on admixture with a sample prepared as in (a).

Cortisone diacetate-3-*cycloethylene-ketal* (Δ⁵-*pregnene*-17α,21-*diol*-11,20-*dione* 3-*cycloethylene ketal diacetate*) (X)

(a) *By ketalization of cortisone diacetate*. A solution of cortisone diacetate (IX) (10 g) in methyl ethyl dioxolane (180 cc) containing *p*-toluenesulfonic acid hydrate (200 mg) was distilled at such a rate that 135 cc of distillate was collected after 1 hr. Water (250 cc) containing sodium carbonate (1·0 g) was then added and the product extracted with benzene. Removal of the solvent afforded a product having λ_{max}^{EtOH} 234–236 mμ, ε 1,950. A solution in benzene (200 cc) was adsorbed onto alumina (500 g). Elution with benzene–ether (80 : 20; 2·5 l.) followed by one crystallization from benzene–ether afforded *cortisone diacetate* 3-*cycloethylene ketal* (X) (5·91 g), m.p. 173–176°, raised by several crystallizations from benzene–ether to 180–182°, $[\alpha]_D$ −20°; X exhibited no selective absorption in the ultraviolet. (Found: C, 66·81; H, 7·21; O, 25·66. $C_{27}H_{36}O_8$ requires: C, 66·37; H, 7·43; O, 26·20%).

(b) *By acetylation of cortisone acetate* 3-*cycloethylene ketal*. Cortisone acetate-3-cycloethylene ketal[20] (VIII) (21·0 g) was added to a suspension of finely divided calcium carbonate (4·0 g) in acetic anhydride (550 cc) and heated under reflux in an atmosphere of nitrogen for 24 hr. After concentrating the solution to approximately 100 cc *in vacuo* the suspension was added to ice water (2· 5l. containing sodium carbonate (125 g). Extraction with ethyl acetate gave a solution which was washed with water, dried (Na_2SO_4), concentrated to 75 cc and the hot solution was then diluted with ether and hexane to afford a crystalline precipitate of the ketal-diacetate (X) (11·9 g) m.p. 167–176°, raised by one crystallization from benzene–ether to 179–182°, undepressed on admixture with a sample prepared as in method (a).

5α,6α-*Oxidopregnane*-17α,21-*diol*-11,20-*dione* 3-*cycloethylene ketal* 17,21-*diacetate* (XI)

A solution of permonophthalic acid (7·0 g) in ether (80 cc) was added at 0° to a solution of the ketal (X) (8·9 g) in chloroform (90 cc). After keeping at 0–5° for 18 hr the solution was washed with water, cold 2% sodium hydroxide solution and finally water. After drying (Na_2SO_4) the solution was evaporated and the product crystallized from acetone–hexane to afford the 5α,6α-*epoxide* (8·0 g) m.p. 225–232°, raised by several crystallizations from benzene–hexane to 232–234°, $[\alpha]_D$ −18°. (Found: C, 64·62; H, 7·19; O, 28·19. $C_{27}H_{36}O_9$ requires: C, 64·27; H, 7·19; O, 28·54%).

6β-*Fluoro*-Δ⁵-*pregnene*-5α,17α,21-*triol*-11,20-*dione* 3-*cycloethylene ketal* 17,21-*diacetate* (XII)

Boron trifluoride etherate (freshly distilled) (5·6 cc) was added to a solution of the α-epoxide (XI) (5·6 g) in benzene–ether (1 : 1; 600 cc). After 3 hr at room temp the solution was washed with water until neutral, evaporated to approximately 100 cc and adsorbed onto alumina (280 g). Elution with benzene–ether (90 : 10; 3 l.) afforded 6β-*fluoro*-Δ⁵-*pregnene*-5α,17α,21-*triol*-11,20-*dione* 3-*cycloethylene ketal* 17,21-*diacetate* (XII) (2·6 g) m.p. 224–229°, raised by several crystallizations from benzene–hexane to 232–234°, $[\alpha]_D$ −9°. (Found: C, 61·81; H, 7·09; F, 3·72. $C_{27}H_{37}O_9F$ requires: C, 61·81; H, 7·11; F, 3·62%).

6β-Fluorocortisone diacetate (XIII)

Dry hydrogen chloride was passed through a solution of 6β-fluoro-Δ^5-pregnene-5α,17α,21-triol-11,20-dione 3-cycloethylene ketal 17,21-diacetate (XII) (3·85 g) in acetic acid (125 cc) at 15° for 25 min. Addition of water and filtration afforded *6β-fluorocortisone diacetate* (XIII) (2·72 g) m.p. 210–214° raised by crystallizations from acetone–hexane to 214–216°, $[\alpha]_D$ +62°, λ_{max}^{EtOH} 232–234 mμ, ε 11,480. (Found: C, 64·93; H, 7·00; F, 4·36. $C_{25}H_{31}O_7F$ requires: C, 64·89; H, 6·75; F, 4·10%).

6α-Fluorocortisone diacetate (Vb)

A solution of 6β-fluoro-Δ^5-pregnene-5α,17α,21-triol-11,20-dione 3-cycloethylene ketal 17,21-diacetate (XII) (600 mg) in acetic acid (40 cc) at 15° was saturated with dry hydrogen chloride and then kept at room temp for 24 hr. Addition of water afforded *6α-fluorocortisone diacetate* (Vb) m.p. 235–240°, raised by chromatography over silica–celite (1 : 1; 30 g) to 268–272° (200 mg). The analytical sample from acetone-hexane had m.p. 270–272°, $[\alpha]_D$ +108°, λ_{max}^{EtOH} 232–234 mμ, ε 16,000. (Found: C, 63·27; H, 6·70; F, 3·90. $C_{25}H_{31}O_7F.1/2\ H_2O$ requires: C, 63·68; H, 6·84; F, 4·03%).

Alkaline hydrolysis of 6α-fluorocortisone diacetate (Vb)

A suspension of the diacetate (Vb) (250 mg) in methanol (2·5 cc) containing potassium hydroxide (25 mg) was stirred at 0° under nitrogen for 1¾ hr. After 1¼ hr a complete solution was obtained. After acidification with acetic acid addition of water and isolation with ethyl acetate gave a product which was dissolved in pyridine (5·0 cc) containing acetic anhydride (0·5 cc) and kept at room temp for 16 hr. Addition of water and isolation with ethyl acetate gave a product which was adsorbed from methylene dichloride onto silica–celite (1 : 1; 25 g). Elution with methylene dichloride–acetone (80 : 20; 300 cc) afforded a fraction which after crystallization from acetone–hexane gave 6α-fluorocortisone acetate (Va) (30 mg) m.p. 207–210°, raised by crystallization from acetone–hexane to 217–219°, undepressed on admixture with an authentic sample. The infrared spectra of the two samples were identical.

6α-Fluoroprednisone diacetate (VIb)

Selenium dioxide (2·5 g) was added to a solution of 6α-fluorocortisone diacetate (Vb) (5·0 g) in t-butyl alcohol (250 cc) containing pyridine (0·8 cc) and heated under reflux in an atmosphere of nitrogen for 24 hr. The reaction mixture was then diluted with ethyl acetate (250 cc) and filtered through celite. After removal of the solvent the residue was triturated with water (500 cc), filtered, dried and crystallized from ethyl acetate–hexane to afford *6α-fluoroprednisone diacetate* (VIb) (2·25 g), m.p. 255–258°, raised by crystallizations from ethyl acetate–hexane to 260–262°, $[\alpha]_D$ +68°, λ_{max}^{EtOH} 236–238 mμ, ε 15,100. (Found: C, 64·85; H, 6·55; F, 3·92. $C_{25}H_{29}O_7F$ requires: C, 65·17; H, 6·35; F, 4·12%).

6α-Fluoro-$\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (XIV)

Methane sulphonyl chloride (1·6 cc) was added to a solution of 6α-fluorohydrocortisone acetate (II) (2·9 g) in dimethyl formamide (24·7 cc) and pyridine (3·4 cc) and then heated at 80° for 1½ hr. Addition of ice water and isolation with ethyl acetate afforded a product which was adsorbed from benzene onto silica–celite (3 : 1; 160 g). Elution with benzene–ether (80 : 20; 1·5 l.) afforded *6α-fluoro-$\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate* (XIV) (2·04 g) m.p. 219–221° raised by crystallizations from acetone to 222–224°, $[\alpha]_D$ +71°, λ_{max} 234–236 mμ, ε 15,850. (Found: C, 68·08; H, 7·17; F, 4·47. $C_{23}H_{29}O_5F$ requires: C, 68·29; H, 7·23; F, 4·69%).

9β,11β-Oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (XV)

N-Bromoacetamide (1·75 g) was added portionwise over 1 hr to a stirred suspension of 6α-fluoro-$\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate (XIV) (3·75 g) in dioxane (37·5 cc) containing 0·46 N perchloric acid (5·6 cc) at 20°. After a further hour at room temp the excess of hypobromous acid was destroyed by the addition of sodium sulphite solution (10%). Ice water was then added and the product was extracted with ether. The combined extracts were washed with water, dried (Na_2SO_4) and the solvent removed at 25° *in vacuo*. Potassium acetate (3·75 g) was then added to a solution of the crude product in acetone (140 cc) and heated under reflux for 18 hr. Removal of the bulk of the solvent on the steam bath, addition of water and filtration gave a product which was

adsorbed from benzene onto silica–celite (3 : 1; 200 g). Elution with benzene–ether (70 : 30; 2·9 l.) afforded the 9β,11β-*epoxide* (XV) (2·65 g) m.p. 198–201° raised by several crystallizations from acetone to 205–206°, $[\alpha]_D$ +60°, λ_{max} 236–238 mμ, ε 12,600. (Found: C, 65·96; H, 7·15; F, 4·86. $C_{23}H_{29}O_6F$ requires: C, 65·69; H, 6·95; F, 4·51%).

6α,9α-*Difluorohydrocortisone acetate* (XVI)

9β,11β-Oxido-Δ^4-pregnene-17α,21-diol-3,20-dione 21-acetate (1·49 g) in methylene dichloride (50 cc) was added with stirring over 10 min to a mixture of anhydrous hydrofluoric acid (2·73 g) and tetrahydrofuran (4·8 g) at −80°. After a further 10 min at −80° the reaction mixture was kept at 0° for 7 hr when it was added to an excess of aqueous sodium bicarbonate solution. Isolation with methylene dichloride gave a product which was dissolved in pyridine (15 cc) and acetic anhydride (2 cc) and heated on the steam bath for 1 hr. Addition of ice water and extraction with ethyl acetate gave a product which was adsorbed from benzene onto silica-celite (3 : 1; 100 g). Elution with benzene–ether (70 : 30; 450 cc) afforded 6α,9α-*difluorohydrocortisone acetate* (XVI) (1·05 g) m.p. 220–222° raised by crystallizations from aqueous methanol to 224–226°, $[\alpha]_D$ +118°, λ_{max} 234 mμ, ε 19,900. (Found: C, 62·98; H, 6·66; F, 8·39. $C_{23}H_{30}O_6F_2$ requires: C, 62·71; H, 6·87; F, 8·63%).

6α,9α-*Difluoroprednisolone acetate* (XVII)

Selenium dioxide (320 mg) was added to a solution of 6α,9α-difluorohydrocortisone acetate (XVI) (640 mg) in t-butyl alcohol (60 cc) containing pyridine (0·08 cc) and heated under reflux with stirring in a nitrogen atmosphere for 40 hr. The precipitate of selenium was removed by filtration through celite and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate (50 cc), washed several times with water, dried (Na_2SO_4) and the solvent was again removed *in vacuo* to afford a product which was adsorbed from benzene onto silica–celite (3 : 1; 30 g). Elution with benzene–ether (70 : 30; 400 cc) afforded 6α,9α-*difluoroprednisolone acetate* (XVII), (210 mg) m.p. 218–222°, raised by crystallizations from acetone–hexane to 224–226°, $[\alpha]_D$ +114°; λ_{max} 238 mμ, ε 15,100. (Found: C, 62·73; H, 6·41; F, 8·22. $C_{23}H_{28}O_6F_2$ requires: C, 62·98 H, 6·43; F, 8·65%).

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ADDENDUM TO Vol. 6, No. 2

1 : 6-Anhydro-D-galactose (Galactosan α⟨1,5⟩ β⟨1,6⟩)*

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VOL. 7 1959

DIE Verfasser obiger Arbeit stellen der pyrolytischen, mit sehr schlechten Ausbeuten arbeitenden Methode[1] ihre Methode, die auf einer Verbesserung der von Montgomery *et al.*[2] beruht, gegenüber. Sie erwähnen nicht, dass das D-Galactosan α⟨1,5⟩ β⟨1,6⟩ erstmalig bereits 1929 von mir[3] in guter Ausbeute aus Acetobrom-D-galactose über das Tetraacetyl-D-galactosido-trimethyl-ammoniumbromid synthetisiert wurde. Einfacher und ebenfalls mit hohen Ausbeuten geht der Weg über die β-1-Fluor-D-galactose, aus der es mit Alkali oder mit basischem Austauscher,[4] in letzterem Falle sofort analysenrein, anfällt.

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* Bemerkungen zu einer Arbeit von A. Fernez und P. J. Stoffyn, *Tetrahedron* **6**, 139 (1959).

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Tetrahedron 1959, Vol. 7, pp. 165 to 172. Pergamon Press Ltd. Printed in Northern Ireland

VOL. 7 1959

EFFECTS OF RING SIZE ON THE REACTIONS OF CYCLIC OLEFINS

HALOHYDRINS FROM METHYLENECYCLOALKANES[1,2]

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Abstract—Addition of HOCl to methylenecycloalkanes (ring sizes C_4 through C_7) gave mixtures of chlorohydrins with abnormal orientation predominating with the 4- and 6-membered ring compounds. Addition of HOBr to these olefins gave 1-bromocycloalkylmethanols as the only bromohydrin product. Cycloalkanecarboxaldehyde, in amounts dependent on ring size, accompanied the formation of bromohydrin from olefin oxide and HBr solution.

An interpretation of these results is included.

As part of a study of the effects of ring size on the reactions of cyclic olefins,[3] we have included additions of hypohalous acids to a series of methylenecycloalkanes (ring sizes C_4 through C_7). Although we observed no orientation effects when hydrogen bromide was the addend,[3b] significant differences among these olefins were obtained with hypohalous acids.

Additions of hypohalous acids to acyclic 1-alkenes occur predominantly or exclusively with normal orientation (primary halogen).[4]

$$R{-}CH{=}CH_2 + HOX \rightarrow R{-}\underset{\displaystyle OH}{\underset{|}{CH}}{-}CH_2{-}X$$

These additions are pictured as stepwise processes initiated by attack of a positive halogen or its kinetic equivalent on the olefin,[4a-b,5] probably through a pi-complex. Electrical effects are generally regarded to be of major importance in determining orientation. Substituted olefins may give rise to abnormal orientation in the halohydrin product,[4c,5] but in the absence of serious steric factors[6] unsubstituted acyclic olefins give very largely (or exclusively) the halohydrin to be expected on the basis of the usual electron-releasing effects of alkyl groups.

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This research was also supported in part by a grant from Research Corporation, to whom our appreciation is extended.

[2] Taken from the Ph.D. dissertation submitted by O. S. Pascual to Louisiana State University, 1956. Reported in part at the 131st Meeting of the American Chemical Society, Miami, April, 1957. A Preliminary Communication appeared in *J. Amer. Chem. Soc.* **79**, 2341 (1957).

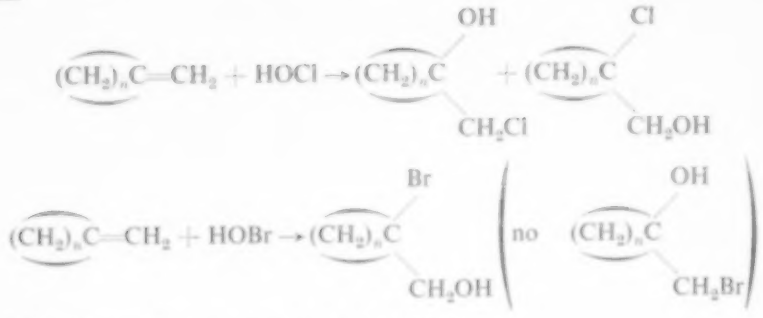
[3] Previous papers in this series include: (a) J. G. Traynham and M. F. Sehnert, *J. Amer. Chem. Soc.* **78**, 4024 (1956); (b) J. G. Traynham and O. S. Pascual, *J. Org. Chem.* **21**, 1362 (1956); (c) J. G. Traynham and J. R. Olechowski, *J. Amer. Chem. Soc.* **81**, 571 (1959).

[4a] J. Hine, *Physical Organic Chemistry* pp. 212–213, McGraw-Hill, New York (1956); [b] P. B. D. de la Mare and A. Salama, *J. Chem. Soc.* 3337 (1956); [c] L. Smith and S. Skyle, *Acta Chem. Scand.* **4**, 39 (1950) and **5**, 1415 (1951).

[5] P. B. D. de la Mare and J. G. Pritchard, *J. Chem. Soc.* 3910 (1954).

[6] W. H. Purterbaugh and M. S. Newman, *J. Amer. Chem. Soc.* **79**, 3469 (1957), report exclusive abnormal addition of the elements of $Br{-}OCH_3$ (from bromine in methanol) to t-butylethylene and some abnormal addition to 1-hexene.

In striking contrast to these results with acyclic alkenes, we have found that addition of HOCl to methylenecycloalkanes gives mixtures of chlorohydrins, with abnormal orientations predominating with the 4- and 6-membered ring compounds,[7] and that addition of HOBr to these olefins gives only abnormally oriented bromohydrins.



The distribution data are summarized in Table 1.

EXPERIMENTAL[8]

Preparations of the *methylenecycloalkanes* have been previously described.[2b]

Authentic 1-*chloromethylcycloalkanols* (except for 1-chloromethylcyclobutanol) were synthesized by the selective hydrolysis of the appropriate 1-chloro-1-chloromethylcycloalkane.[9] Suspensions of approximately equal molar quantities of olefin dichloride and $CaCO_3$ in water were refluxed for 6 hr.[13] Appreciable amounts of the dichloride were removed from the insoluble organic material along with low yields (28–39%) of the chlorohydrin (primary chloride). These chlorohydrins all gave precipitates with NaI in acetone and with alcoholic $AgNO_3$ (slowly), produced immediate cloudiness with Lucas reagent, reduced $KMnO_4$ and showed infrared absorption near 7·25 μ (tertiary alcohol). Physical properties are given in Table 2.

1-*Chlorocycloalkylmethanols*. Methylenecycloalkane oxides were prepared by treatment of the halohydrin with aqueous KOH or, in the case of methylenecyclohexane oxide, as by-product in the preparation of cycloheptanone from cyclohexanone and diazomethane:[14] methylenecyclobutane

[7] Formation of 1-chlorocyclohexylmethanol only from methylenecylohexane and HOCl has been reported by M. Tiffeneau, P. Weill and B. Tchoubar, *Compt. rend.* **205**, 144 (1937).

[8] Atomic refractions for calculation of MR and chemical classification tests taken from R. L. Shriner, R. C. Fuson and D. Y. Curtin, *The Systematic Identification of Organic Compounds* (4th Ed.). John Wiley, New York (1956).

[9] Prepared in poor yields by the addition of chlorine to chilled solutions of olefins in CCl_4. Although the addition of bromine to these methylenecycloalkanes gave the expected dibromides in fairly good yields, the product mixtures from chlorine additions contained considerable amounts of polymeric material and some chloromethylcycloalkene. (Similar results were obtained with chlorine and methylenecyclohexane in the presence of solid $NaHCO_3$ by Arnold and Lee.[10]) The dichlorides isolated were: 1-chloro-1-chloromethylcyclobutane,[11] b.p. 49–50° (14 mm), n_D^{20} 1·4777, d_4^{20} 1·175; 1-chloro-1-chloromethylcyclopentane, b.p. 55–56° (7 mm), n_D^{20} 1·4982, d_4^{20} 1·191, MR_{calc} 37·4, MR_{expt} 37·7; 1-chloro-1-chloromethylcyclohexane,[10] b.p. 85–87° (15 mm), n_D^{20} 1·4915, d_4^{20} 1·169; and 1-chloro-1-chloromethylcycloheptane, b.p. 61–62° (3·3 mm), n_D^{20} 1·4910, d_4^{20} 1·105, MR_{calc} 46·7, MR_{expt} 47·5.

Methylenecyclobutane gave, in addition to the desired dichloride, 2 other products whose molar refractivities agreed fairly well with structure assignments based on the detailed study[12] of bromine addition to methylenecyclobutane: 1,1-*bis*(chloromethyl)cyclopropane, b.p. 56–57° (14 mm), d_4^{20} 1·180, n_D^{20} 1·4832, MR_{calc} 33·5, MR_{expt} 33·7; and 1,2,4-trichloro-2-chloromethylbutane, b.p. 55–56° (6 mm), d_4^{20} 1·305, n_D^{20} 1·4945, MR_{calc} 44·7, MR_{expt} 46·9. These products gave precipitates with NaI in acetone but did not reduce $KMnO_4$ nor show infrared absorption characteristic of olefins.

[10] R. T. Arnold and W. W. Lee, *J. Amer. Chem. Soc.* **75**, 5396 (1953).

[11] N. J. Demjanow and N. Dojarenko, *Ber.* **55B**, 2730 (1922).

[12] D. E. Applequist and J. D. Roberts, *J. Amer. Chem. Soc.* **78**, 874 (1956).

[13] C. E. Sparks and R. E. Nelson, *J. Amer. Chem. Soc.* **58**, 1010 (1936).

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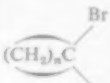
VOL. 7 1959

TABLE 1. PRODUCT DISTRIBUTIONS IN HYPOHALOUS ACID ADDITIONS TO METHYLENECYCLOALKANES

Ring size	Hypochlorous acid				Hypobromous acid		
	Total yield %	Proportion of total			Total yield %	Proportion of total	
				Other product			Other products
4	72	60	40	none[a]	78	99	1[b]
5	64	41	58	1[b]	67	91	9[c]
6	92	67	32	1[b]	89	98	2[d]
7	86	35	64	1[b]	87	87	13[d]

[a] No rearrangement products were found. [b] Slight absorption attributable to a carbonyl group (probably in cycloalkanecarboxaldehyde) appeared in the infrared spectrum of the product. [c] Methylenecyclopentane oxide. [d] Cycloalkanecarboxaldehyde.

TABLE 2. PHYSICAL PROPERTIES OF METHYLENECYCLOALKANE HALOHYDRINS

Compound[a]	B.p. (mm)	d_4^{20}[b]	n_D^{20}[b]	MR	
				calc.	expt.
$ClCH_2—C_4—OH$[11]	56–60°	—	—		
	(20)	1·135	1·4688	30·0	29·6
$Cl—C_4—CH_2OH$	69–70°	1·154	1·4760	30·0	29·5
	(20)	1·153	1·4765		29·5
$ClCH_2—C_5—OH$	57–58°	1·143	1·4841	34·1	33·7
	(6)	1·144	1·4834		33·6
$Cl—C_5—CH_2OH$	62–63°	1·182	1·5036	34·1	33·7
	(3)	1·183	1·5038		33·7
$ClCH_2—C_6—OH$	54–55°	1·127	1·5024	38·7	38·9
	(4)	1·128	1·5030		39·0
$Cl—C_6—CH_2OH$[7]	53–54°	1·113	1·4905	38·7	38·6
	(2)	1·113	1·4910		38·7
$ClCH_2—C_7—OH$	56–58°	1·118	1·4997	43·3	42·8
	(2)	1·119	1·4990		42·7
$Cl—C_7—CH_2OH$	70–71°	1·128	1·5114	43·3	43·2
	(2)	1·127	1·5110		43·2
$Br—C_4—CH_2OH$	64–65°	1·506	1·5041	32·9	32·5
	(10)	1·506	1·5036		32·4
$Br—C_5—CH_2OH$	45–46°	1·463	1·5126	37·0	36·8
	(2)	1·463	1·5126		36·8
$Br—C_6—CH_2OH$[7]	55–56°	M.P. 82–83°	—		—
	(2)				
$Br—C_7—CH_2OH$	73–74°	1·339	1·5232	46·2	47·3
	(3)	1·340	1·5225		47·2

[a] C_4, C_5, etc., represent cycloalkylidine structures with the number of ring carbons indicated.
[b] The first value in each case is that for independently synthesized ("authentic") halohydrin; the second value is that for the product obtained by hypohalous acid addition to the olefin.

oxide,[11] b.p. 90–92° n_D^{20} 1·4207; methylenecyclopentane oxide, b.p. 43–44° (62 mm) n_D^{20} 1·4290, d_4^{20} 0·923, MR_{calc} 27·5, MR_{expt} 27·4; methylenecyclohexane oxide,[14] b.p. 62–63° (37 mm), n_D^{20} 1·4470; methylenecycloheptane oxide, b.p. 84–85° (40 mm), n_D^{20} 1·4552, d_4^{20} 0·938, MR_{calc} 36·8, MR_{expt} 36·5. The olefin oxide (0·01–0·06 mole) was dripped into conc HCl (20 ml) chilled below 5°. The mixture was stirred for an hour and then poured onto ice. Conventional work-up gave poor yields of chlorohydrins whose physical and chemical properties were different from those of the isomeric chlorohydrins described above. These 1-chlorocycloalkylmethanols all gave precipitates with alcoholic $AgNO_3$ (immediately) but none with NaI in acetone, reduced $KMnO_4$, gave negative Lucas tests and showed no infrared absorption near 7·25 μ. Physical properties are given in Table 2.

1-*Bromocycloalkylmethanols*. These bromohydrins were prepared from the olefin oxides and chilled 48% hydrobromic acid. After addition of the oxide was completed and stirring had been continued for an hour longer, the acid was neutralized with solid Na_2CO_3. The mixture was extracted with ether, the ether solution was washed and dried, and the ether was removed by distillation. Distillation of the residue gave the bromohydrins, whose physical properties are listed in Table 2. Each of the bromohydrins formed an immediate precipitate with alcoholic $AgNO_3$ and gave negative tests with Lucas reagent and with NaI in acetone. Acid hydrolysis (refluxing for 5–6 hr with 5 M HCl) of the bromohydrins (5-, 6- and 7-membered rings) gave good yields of the corresponding cycloalkanecarboxaldehydes. These aldehydes had the following properties: cyclopentanecarboxaldehyde,[15] b.p. 55–56° (36 mm), d_4^{20} 0·920, n_D^{20} 1·4343, semicarbazone[15] m.p. 123–124°; cyclohexanecarboxaldehyde,[16] b.p. 49·5° (10 mm), d_4^{20} 0·930, n_D^{20} 1·4490, 2,4-dinitrophenylhydrazone[16] m.p. 172–173°; cycloheptanecarboxaldehyde,[17] b.p. 45·5–46° (4 mm), n_D^{20} 1·4621, semicarbazone[17] m.p. 154–155°.

Except for the preparation from methylenecyclobutane oxide, the initial product mixtures from the olefin oxides contained appreciable amounts of cycloalkanecarboxaldehyde in addition to the bromohydrin. The composition of the residue after evaporation of ether solvent was evaluated by comparison of its infrared spectrum with spectra of known mixtures prepared from distilled samples of 1-bromocycloalkylmethanol and cycloalkanecarboxaldehyde. Fractional distillation of the residue afforded pure samples of bromohydrin and aldehyde as well as confirmation of the spectral analysis.

Table 3 summarizes the data on product compositions. Such a small amount of methylenecyclobutane oxide was used that no product other than bromohydrin could be isolated.

TABLE 3. PRODUCT FROM OLEFIN OXIDES AND HBr

Ring size	Total yield, %	% Bromohydrin	% Aldehyde
5	45	65	35
6	68	95	5
7	87	68	32

Hypohalous acid solutions. HOCl[18] and HOBr[19] solutions were prepared by adding the halogen to well-stirred, chilled aqueous suspensions of HgO or Ag_2SO_4, respectively. The approximately 1·8 M solutions were distilled at reduced pressure in the dark (bath temperature about 40°) and the exact concentrations were determined iodometrically. Because we found that the use of concentrated HOCl solutions sometimes led to the formation of side products, the amount of HOCl solution required for each addition reaction was diluted to 500 ml before use.

HOBr was also formed *in situ* by the hydrolysis of N-bromosuccinimide.[20]

[13] G. R. Clemo and J. Ormston, *J. Chem. Soc.* 362 (1933).
[16] I. Heilbron, E. R. H. Jones, R. W. Richardson and F. Sondheimer, *J. Chem. Soc.* 739 (1949).
[17] W. Reppe, O. Schlichting, K. Klager and T. Toepel, *Liebegs Ann.* **560**, 62 (1948).
[18] A. Chung and G. C. Israel, *J. Chem. Soc.* 2668 (1955).
[19] S. J. Branch and B. Jones, *J. Chem. Soc.* 2323 (1954).
[20] C. O. Guss and R. Rosenthal, *J. Amer. Chem. Soc.* **77**, 2549 (1955).

Hypohalous acid additions. To a well-stirred, chilled (below 15°) suspension of methylenecycloalkane (approx. 0·12 mole) in water (200 ml) was added about 1/5 of slightly more than the theoretical amount of freshly-distilled, cold hypohalous acid solution. When the mixture no longer turned acidified starch-iodide paper blue, a second portion of hypohalous acid solution was added. The process was repeated until all the hypohalous acid solution had been added. The mixture was stirred for an hour longer and saturated with NaCl. The lower layer was separated, washed with dilute $NaCO_3$ solution and dried with $MgSO_4$. The infrared spectrum and refractive index of this organic material were taken.

The combined aqueous material was extracted with ether to recover the remainder of the product. All of the organic material was fractionally distilled through a Claisen still-head having a vacuum-jacketed Vigreux column approximately 12 × 140 mm. The product components were identified by comparison of their physical and chemical properties and infrared spectra with those of authentic samples synthesized independently.[21]

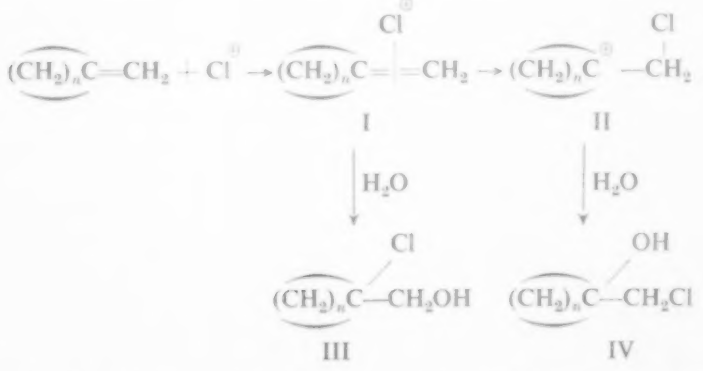
Comparison of the infrared spectrum of the crude product mixture with those of known mixtures prepared from authentic product samples as well as proportions of distillate in the fractions collected afforded data from which product distributions could be estimated. These data are summarized in Table 1.

A suspension of N-bromosuccinimide in water[20] could be substituted for HOBr solution without affecting product distributions.

HOBr *with isobutylene.* Although isobutylene bromohydrin has been prepared in poor yield from isobutylene and an aqueous solution of bromine and bromide,[19] there does not appear to be any report of the addition of relatively pure HOBr solution. Treatment of isobutylene (0·16 mole) with HOBr solution gave a 77% yield of product which was at least 97% 1-bromo-2-methyl-2-propanol[22] (b.p. 66–62·5° (31 mm), d_4^{20} 1·451, n_D^{20} 1·4722) and no more than 3% material tentatively identified as the isomer, 2-bromo-2-methyl-1-propanol.

DISCUSSION OF RESULTS

Attack on an olefin by a positive halogen will lead to an intermediate with carbonium character and with the halogen normally attached to the less substituted carbon.[4a] The data in Table 1 clearly indicate that ring size in these *exo*-olefins has an effect on the orientation in HOCl addition. The preponderance of abnormally oriented chlorohydrins from the 4- and 6-membered rings is consistent with the view that trigonal carbons in those rings are less favored than in 5- and 7-membered ones.[23] Possible reaction paths are indicated in the following equations:

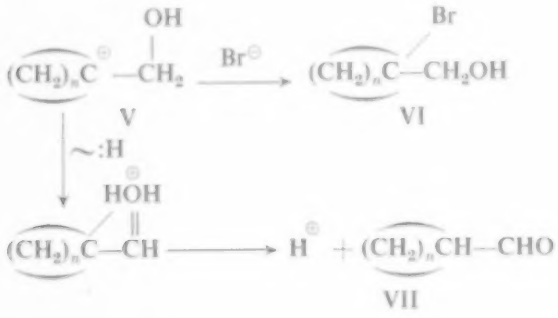


[21] Although no authentic 1-chloromethylcyclobutanol was prepared independently, the product assigned this name had chemical properties similar to those of the other normal chlorohydrins (primary chloride, tertiary alcohol) and the physical and spectral properties were consistent with the structure assignment.
[22] C. M. Suter and H. D. Zook, *J. Amer. Chem. Soc.* **66**, 741 (1944).
[23] H. C. Brown, J. H. Brewster and H. Shechter, *J. Amer. Chem. Soc.* **76**, 467 (1954).

The initially formed pi-complex (I) may rearrange as usual to the conventional carbonium ion (II),[4a–b,5,24] or it may suffer direct attack by water to give III, the abnormally oriented product. The carbonium ion II combines with water to give the normally oriented chlorohydrin IV.

Rearrangement of I to II is the less favored path for 4- and 6-membered rings because of the tendency to pass from trigonal to tetrahedral carbons in those rings,[23] but is satisfactory for 5- and 7-membered rings.[25] The formation of large amounts of III even from 5- and 7-membered rings, when acyclic olefins give corresponding products only in small amounts, indicates that this explanation is incomplete and suggests an importance of the ring structure itself in directing orientation.

The proportions of aldehyde and bromohydrin obtained in the treatment of methylenecycloalkane oxides with HBr (see Table 3) give further support to the claim that the relative stabilities of intermediates containing ring trigonal carbon atoms are strongly influenced or determined by ring size. The olefin oxide reacts with acid to give a carbonium ion intermediate (V) which combines with bromide to give bromohydrin.



V may also rearrange by hydride migration to give cycloalkanecarboxaldehyde (VII). Under the conditions used in these experiments (excess conc HBr), bromohydrin formation is the faster process and aldehyde formation becomes appreciable only when the intermediate V is sufficiently unreactive (long-lived) to allow the slower hydride migration to compete. The intermediate carbonium ion derived from methylenecyclohexane is the most reactive and very little aldehyde appears in the product mixture. The intermediates from methylenecyclopentane and methylenecycloheptane however are longer-lived, hydride shift can compete better, and aldehyde constitutes about 1/3 of the product obtained. Only relatively small changes in energy are required to effect these product proportion changes. Our data for methylenecyclobutane oxide are insufficiently complete to permit evaluation in that case.

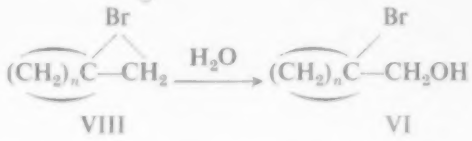
In the HOBr additions however, ring *size* does not seem to play any role in determining orientation. Only a single bromohydrin was obtained from each methylenecycloalkane. The orientation was opposite to that obtained with the

[24] Rearrangement of the protonated olefin (pi-complex) to a more conventional carbonium ion has been shown to be an important part of acid-catalyzed hydration; R. W. Taft, Jr., *J. Amer. Chem. Soc.* **74**, 5372 (1952); R. W. Taft, Jr., E. L. Purlee, P. Riesz and C. A. De Fazio, *J. Amer. Chem. Soc.* **77**, 1584 (1955).

Recent experiments in This Laboratory suggest that the same type of rearrangement is involved in halogen addition to olefins; J. G. Traynham and J. E. Landry, unpublished results.

[25] A more complete discussion of this point is found in reference 3b.

acyclic analog, isobutylene. Here again is an indication that the ring structure itself has an importance in directing orientation. Because of the prevalence of neighboring group participation with bromine, in contrast to the poor participation by chlorine,[26] an additional intermediate (VIII) may be pictured for additions of HOBr (or other reagents involving attack by $Br^{\oplus}$.)



VIII VI

Attack by water molecule on VIII (with Br symmetrically placed between the carbons) would occur far more readily at the primary carbon than at the tertiary one. Bromine in VIII is not necessarily symmetrically placed between the two carbons however, and the tertiary carbon might carry a higher proportion of positive charge than the primary one.[27] Attack would then occur preferentially at the tertiary carbon. This seems to be the case with isobutylene from which normally oriented bromohydrin (by attack on the tertiary carbon) is formed almost exclusively. The role of the ring structure may then be to bring the bromine in an intermediate such as VIII into a more symmetrical position or to make the partially-formed bond between bromine and the ring carbon more resistant to cleavage. The fact that VIII is spirane-like may play a significant part in determining the subsequent fate of such intermediates.

The addition of HOBr to some $\Delta^{9,11}$ unsaturated steroids has been reported to give abnormally oriented bromohydrins.[28] These polycyclic compounds are relatively rigid systems and conformations are quite well fixed. In the cases reported, HOBr addition follows the generalization that intermediates containing 3-membered rings react to open that ring with preservation of the axial bond.[29] The axial bond to Br in an intermediate similar to VIII is preserved even if that means formation of abnormally oriented product.

The formation of an axial bond between the ring carbon and bromine in the intermediate VIII may then be responsible for the exclusive formation of VI from methylenecyclohexane. The classification of axial bonds is less distinct in the other rings used here, but similar considerations may apply. To the extent that chlorine is able to form bridged ions[26,27] the same tendency to preserve the axial bond could account for some of the abnormal chlorohydrins formed. The normal cleavage of the tertiary carbon–oxygen bond in reaction of the epoxides with strong acid contrasts with the unexpected formation of the tertiary carbon-bromine bond in HOBr addition to the olefins. The quite different behavior of the conjugate acid of the epoxides and the analogous intermediate VIII may mean that the ring carbon–oxygen bond in the epoxides is not axial or, more probably, that considerably more bond-breaking has occurred in the transition state derived from the oxygen-containing intermediate than in that from the bromine-containing one.

[26] S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.* **70**, 828 (1949).
[27] An unsymmetrical bridged ion with chlorine has been used to account for the two products obtained from HOCl and allyl chloride; P. B. D. de la Mare and J. G. Pritchard, *J. Chem. Soc.* 3990 (1954).
[28] L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, *J. Amer. Chem. Soc.* **76**, 5017 (1954); E. M. Hicks, Jr. and E. S. Wallis, *J. Biol. Chem.* **162**, 641 (1946).
[29] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **X**, 44 (1956).

Since abnormal products were not obtained from the methylenecycloalkanes with HBr as addend,[3b] it appears that size (or activity[30]) of the attacking cation may have an important role in determining the actual orientation with these olefins. This role may well be associated with the ability to form bridged ion intermediates.[31] We are continuing studies of additions to cyclic olefins in the hope of unveiling more explicit information about these effects.

[30] H. C. Brown and K. L. Nelson, *J. Amer. Chem. Soc.* **75**, 6292 (1953).
[31] A similar suggestion has been made to account for the different amounts of abnormal product obtained from allyl chloride with HCl, HOCl and ICl.[37]

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VOL. 7 1959

GROUP TRANSFER AND RING CONTRACTION PHENOMENA IN THE D-HOMOSTEROID SERIES[1]

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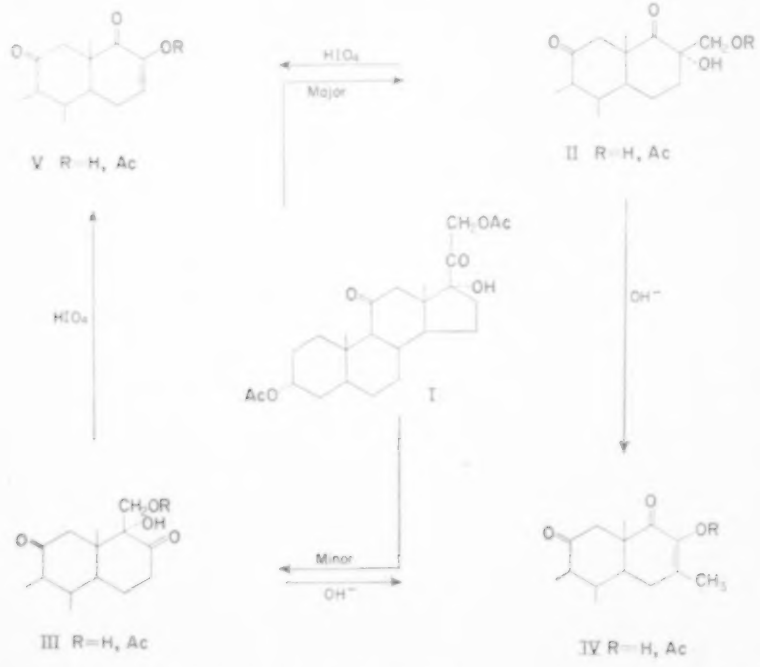
(*Received* 25 *March* 1959)

Abstract—The D-homoketols arising from 17,21-dihydroxy-20-ketosteroids with aluminum alkoxides were observed to undergo alkaline catalyzed rearrangement with group transfer to yield diosphenols. The latter on more vigorous alkaline treatment suffered unidirectional benzilic acid ring contraction to afford 17β-hydroxyisoetianic acids. In the presence of formaldehyde and alkali, on the other hand, these same diosphenols were initially hydroxymethylated followed by ring-contraction to lactones.

IN an earlier account the D-ring expansion of 17α-hydroxy-21-acetoxy cortical systems with Lewis acids was shown to give 17a-ketonic systems as the major product.[2] Under these conditions 3α,17α,21-trihydroxypregnane-11,21-dione-3,21-diacetate (I) provided the 17a-ketone (II, R = Ac) as the major product accompanied by the 17-ketone (III, R = Ac) as the minor component. Room temperature alkaline



[1] A preliminary account of certain aspects of this work was communicated earlier. N. L. Wendler and D. Taub, *Chem. & Ind.* 415 (1958).
[2] N. L. Wendler and D. Taub, *Chem. & Ind.* 822 (1957); *J. Amer. Chem. Soc.* **80**, 3402 (1958).

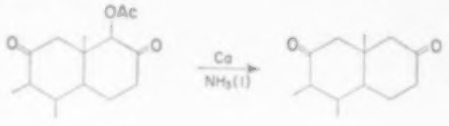
hydrolysis of II (R = Ac) and III (R = Ac) provided the corresponding 3α,17α,21- and 3α,17aα,21-triols respectively. The latter triols on periodate cleavage both afforded the diosphenol V, in turn oxidizable by potassium permanganate to the known etiobilianic acid X.[3] The diosphenol (V) was also synthesized by an independent route emanating from the 17a-ketone (VI).[4] The latter was brominated and the bromo derivative (VII) converted with aqueous alkali in tetrahydrofuran to the ketol (VIII) and/or its positional isomer (IX, R = R′ = H). Copper acetate oxidation of the resultant ketol afforded diosphenol (V, R = H) identical with that obtained from the periodate cleavage of the D-homoketols II and III.

The configuration of the bromoketone VII was shown to be predominantly equatorial by bromination of the parent compound VI (R = H) and determination

of its infrared spectrum; the latter indicated not only the 11C=O at 5·83 μ but also a band at 5·76 μ of nearly the same intensity characteristic of a carbonyl group displaced in band position by an equatorial bromine.[5] The 3-monoacetate VIII and/or IX (R = Ac; R′ = H) was obtained by room temperature hydrolysis of VII (R = Ac) in tetrahydrofuran with aqueous 50 per cent potassium hydroxide in a two-phase system. This product exhibited in its infrared spectrum a single OH band at 2·84 μ characteristic of an equatorial ketol hydroxyl function. If the ketolic hydroxyl function had been axial, a double peak at 2·78 μ and 2·85–2·9 μ would have been anticipated.[5] This product, VIII and/or IX (R = Ac; R′ = H), was converted to its diacetate derivative, VIII and/or IX (R = R′ = Ac) with acetic anhydride in pyridine. The latter appeared to be an isomeric mixture inasmuch as it could not be

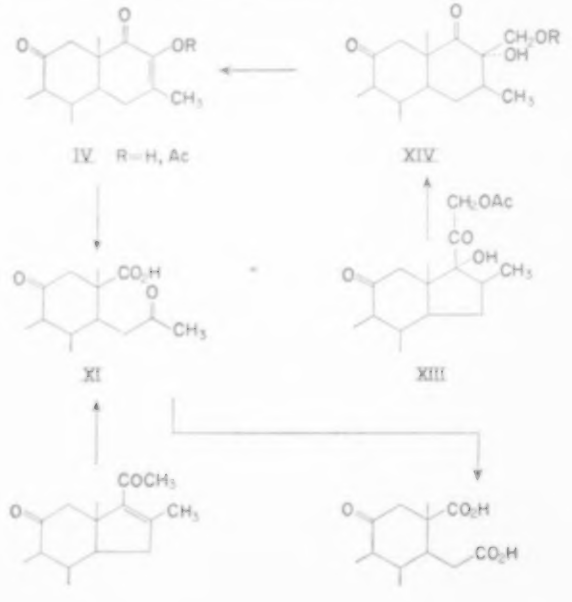
[3] N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, *J. Amer. Chem. Soc.*, **78**, 5027 (1956).
[4] N. L. Wendler, D. Taub and H. L. Slates, *J. Amer. Chem. Soc.* **77**, 3559 (1955).
[5] R. W. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2828 (1952).

separated by chromatography into sharp melting fractions. Reduction of the latter with calcium in liquid ammonia according to the Glaxo procedure[6] produced the 17-ketone (Xa) as the only identifiable product. The amount of Xa formed, however, was insufficient to permit a meaningful estimation of the content of its precursor IX in the original ketol equilibrium.



IX (R = R' = Ac) Xa

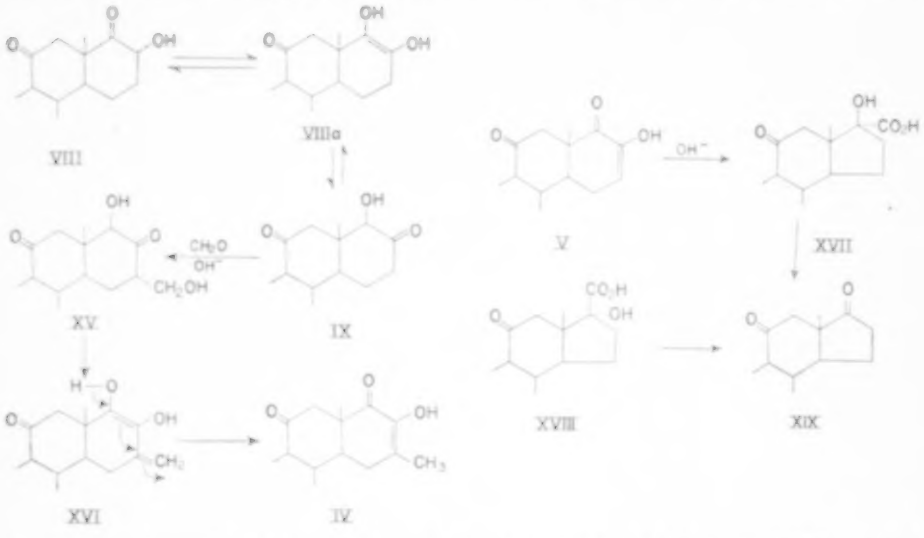
Treatment of both D-homo isomers II and III with hot 10 per cent methanolic potassium hydroxide evoked a unique transfer of the hydroxymethyl group leading to the diosphenol (IV). The structure of this methyl diosphenol (IV) was variously established. Oxidation, for example, of its acetate derivative with potassium permanganate afforded the methyl ketonic acid (XI) identical by infrared comparison with a sample prepared from the 16-methyl-Δ^{16}-20-ketone (XII)[7] by similar oxidation. The methyl ketonic acid (XI) could be oxidized further with sodium hypoiodite to iodoform and the etiobilianic acid (X). By another approach 3α,17α-dihydroxy-21-acetoxy-16β-methylpregnane-11,20-dione (XIII)[7a] was D-homoannulated with aluminum alkoxide to the 17a-ketone (XIV). The latter on hydrolysis and cleavage with periodate yielded the methyl diosphenol (IV).



[6] J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, *J. Chem. Soc.* 4344 (1956).

[7] [a] D. Taub, R. D. Hoffsommer, H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.* **80**, 4435 (1958); E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *Ibid.* **80**, 4428 (1958); [b] H. L. Slates and N. L. Wendler, *Ibid.* In press.

The formation of the methyl diosphenol (IV) ostensibly results from the loss of formaldehyde from II and III through retroaldolization, followed by recombination at position C-16 with the tautomerized ketol (IX). β-Elimination of water from the intermediate XV followed by hydrogen redistribution leads to IV. Substantiation for this mechanism was provided by the synthesis of IV through controlled condensation of the ketol (IX) with formaldehyde. In contrast to the synthesis of the methyl diosphenol from the ketol IX and formaldehyde, however, its formation from the redistribution reaction of the D-homo ketols II and III is an exceedingly efficient process. This fact is suggestive of an intramolecular transfer type reaction in the



latter case; however, an internal group transfer is lacking in a convincing route for execution. The reservation is held, nevertheless, that in the dissociation–recombination sequence, the formaldehyde residue never becomes separated to the extent that subsequent reaction is truly extramolecular in character.

When the diosphenols IV and V were heated for extended periods of time with 20 per cent methanolic potassium hydroxide[8] they suffered ring contraction to yield, in nearly quantitative yield and stereoselective manner, the corresponding 17β-hydroxy isoetianic acids.[9] The 17-iso configuration of the carboxyl function was adduced from the configuration as established in the unmethylated series. Thus, the acid (XVII) obtained from ring contraction of V was different from the known C_{17}-epimeric 3α,17α-dihydroxy-11-ketoetianic acid (XVIII)[10]; both acids, however, on esterification with diazomethane followed by successive reduction with lithium aluminum hydride and cleavage with periodate produced 3α,11β-dihydroxy-5β-androstane-17-one. The latter on acetylation at C_3 followed by oxidation at C_{11} gave 3α-acetoxy-5β-androstane-11,17-dione (XIX). It follows unequivocally therefrom that the acids formed by

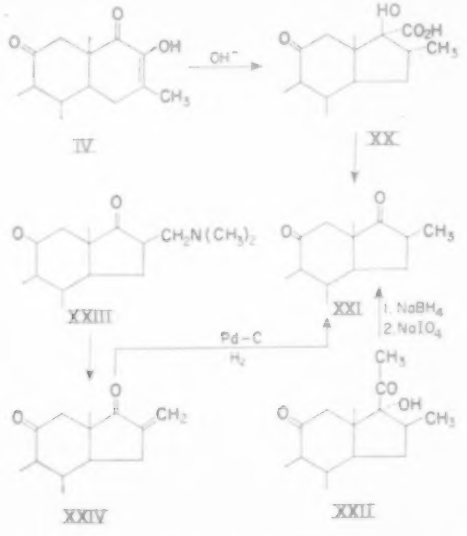
[8] Concentration of alkaline solutions of the diosphenols *in vacuo* under baking conditions at 100° also serves to produce this change.

[9] The preparation of the diosphenol (IV), under the relatively milder conditions of alkaline treatment of the D-homo ketols II and III, is always accompanied by varying amounts of the corresponding 17β hydroxyetianic acid resulting from ring contraction of IV.

[10] L. H. Sarett, *J. Biol. Chem.* **162**, 601 (1946).

alkaline ring contraction of the D-ring diosphenols possess the 17-iso configuration of the carboxyl functions. Recently Georgian and Kundu,[11] working in another series reached the same conclusions with regard to the directional course of the ring contraction process.

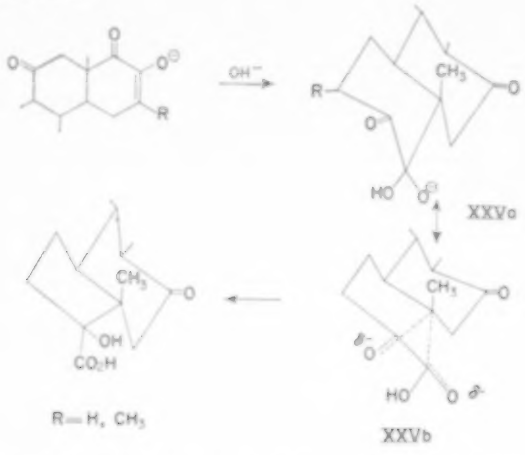
Structure proof for the acid (XX) derived from the methyl diosphenol (IV) as well as additional structural confirmation for the latter itself was provided in the following manner: The acid in the form of its methyl ester was reduced with lithium aluminum hydride followed by cleavage with periodate to 3α,11β-dihydroxy-16β-methyl-5β-androstane-17-one. Acetylation of the latter at C_3 followed by oxidation with chromic acid at C_{11} provided the 11,17-dione (XXI). The latter was identical with a sample prepared by hydrogenation of 3α-acetoxy-16-methylene-5β-androstane-11,17-dione (XXIV). The latter was prepared in turn according to the method of Julian *et al.*[12] via the Mannich reaction on 3α-acetoxy-5β-androstane-11, 17-dione to yield XXIII; β-elimination of dimethylamine from the Mannich base afforded the methylene ketone (XXIV). The foregoing transformations establish the presence of a 16-methyl group in the diosphenol as well as its acid. Further, assuming the hydrogenation to obey the generalized rule-of-the-rear it follows that the configuration of the methyl group in the acid XX is 16β. The latter conclusion is also confirmed by the transformation of 3α,17α-dihydroxy-16β-methylpregnane-11, 20-dione (XXII)[5] by reduction and oxidative cleavage to XXI.



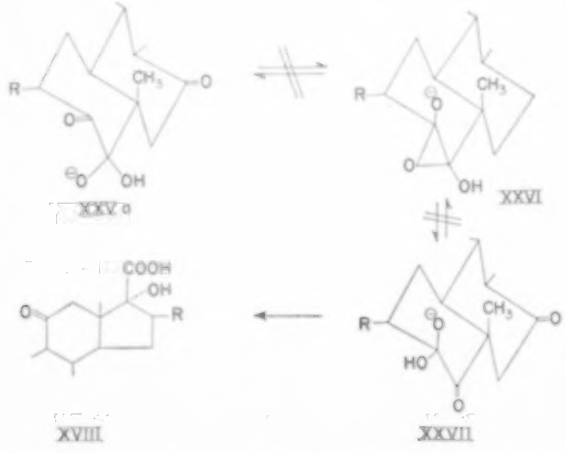
The unidirectional character and consequently the stereoselective nature of the benzilic acid contraction of the diosphenols follows logically from the fact that in alkaline solution they are largely, if not entirely, present as the C_{17}-oxygen anions. Consequently the C_{17a}-carbonyl offers the better acceptor site for hydroxide ion. With addition of hydroxide ion at C_{17a}, the enolization potential of the diosphenol

[11] V. Georgian and N. Kundu, *Chem. & Ind.* 1322 (1958).
[12] P. L. Julian, E. W. Meyer and H. C. Pruity, *J. Amer. Chem. Soc.* **70**, 3872 (1948); F. Newmann, O. Mancera, G. Rosenkranz and F. Sondheimer, *Ibid.* **77**, 5676 (1955).

disappears[13] and the stereochemical fate of the acid resulting from ring contraction is consequently decided. This may best be visualized from the charge distribution state indicated by XXVb.



The possibility of an interconversion of the C_{17a} adduct (XXVa) with a C_{17}-adduct (XXVII), via a form such as XXVI for example, appears excluded by the unidirectional course of rearrangement. If the interconversion of XXVa with XXVII had been significant, a mixture of C_{17}-isomeric etianic acids would have resulted. In actuality the product was exclusively the 17-iso form insofar as could be determined.[14] It is



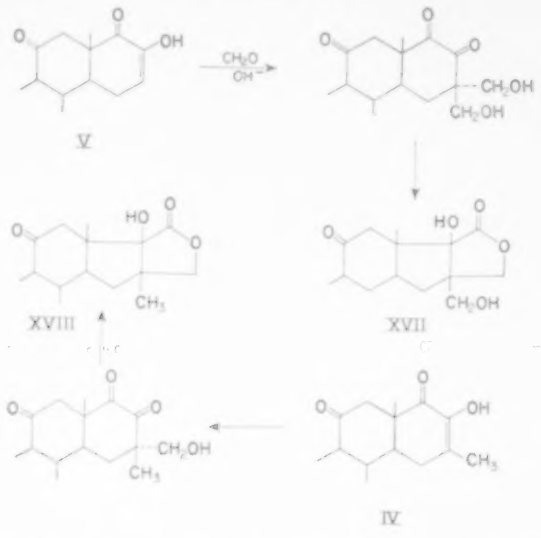
also noteworthy that in the collapse of the diosphenol enolate, consequent to OH-addition at C_{17a}, the methyl substituent at C_{16} assumes the more stable equatorial configuration as was to be anticipated. The latter consequence has been established by the structure clarification leading to the 16β-methyl ketone (XXI).

[13] The carbonyl groups in a cyclohexane 1, 2-dione face essentially in the same direction with corresponding repulsion of adjacent dipole charges. Enolization relieves both the steric instability as well as the adjacent charge repulsion. G. Baddeley, *Ann. Rep. Chem. Soc.* **LII**, 131 (1956).

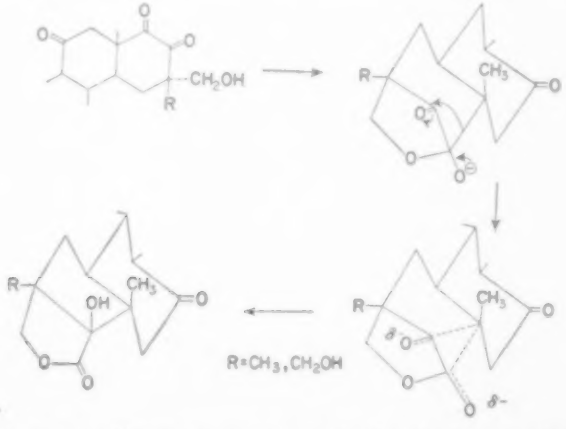
[14] This observation was also made by Georgian and Kundu.[11]

VOL. 7 1959

In the synthesis of the methyl diosphenol (IV) by hydroxymethylation of the ketol (IX) with alkaline formaldehyde (IX → IV), unless careful control of the formaldehyde concentration is maintained a high melting lactone results; the same lactone is also formed from the methyl diosphenol itself on treatment with alkaline



formaldehyde and the latter consequently represents an intermediate in this transformation. A related lactone arises similarly from the unsubstituted diosphenol (V) with alkaline formaldehyde. Both of these lactones are formed in consequence to hydroxymethylation of the respective diosphenols followed by benzilic acid ring



contraction. It is reasonable to assume not only that hydroxymethylation proceeds according to the generalized rule-of-the-rear but also that the subsequent benzilic acid contraction occurs internally, thereby predetermining the geometry of the products as being stereochemically the same as that of their 17-isoetianic acid counterparts.

EXPERIMENTAL[15]

D-Homoannulation of 3α,21-diacetoxy-17α-hydroxy pregnane-11,20-dione

(I) *With aluminum alkoxide.* A solution of 27·5 g (I) in 300 cc dioxane and 950 cc toluene was treated with 180 cc cyclohexanone. The mixture was distilled until 100 cc distillate had been collected; 6 g aluminum isopropoxide was added and the reaction mixture refluxed for 2·5 hr in a nitrogen atmosphere. The reaction mixture was allowed to stand overnight. Water was added and the solvents were evaporated *in vacuo*, the process being repeated several times until a gum was deposited. The residue was treated with 75 cc conc. HCl in an equal vol water and the organic material extracted with ethyl acetate. The ethyl acetate extract was washed successively with dil potassium bicarbonate solution, water and saturated sodium chloride solution. The washed ethyl acetate layer was dried and concentrated *in vacuo* to an oil which partially crystallized. Separation of the crystals and recrystallization from acetone–ether afforded 8 g pure *3α-acetoxy-17α-hydroxy-17β-acetoxymethyl-5β-D-homoandrostane-11,17a-dione* II (R = Ac) m.p. 172–174°, $[\alpha]_D$ +88·1°.

Found: C, 66·73; H, 8·01. Calc. for $C_{23}H_{34}O_7$: C, 66·94; H, 8·09%)

The mother liquors from the separation of II were chromatographed on 500 g acid-washed alumina and the eluates consisting of 1–2% ether in benzene afforded an additional 4·5 g crystalline II making a total of 12·5 g of the 17a-ketone (78% of the isomer content). The eluates 5–50% ether in benzene afforded 3·5g crystalline *3α-acetoxy-17aα-hydroxy, 17aβ-acetoxy methyl, 5β-D-homandrostane-11,17-dione* (III) (R = Ac) (22% of the isomer content), m.p. 202–204°, $[\alpha]_D$ +26·5°.

(Found: C, 66·62; H, 8·02. Calc. for $C_{23}H_{36}O_7$: C, 66·94; H, 8·09%).

Cold alkaline hydrolysis of the D-homo ketol diacetates II *and* III (R = Ac)

A solution of 4·48 g II (R = Ac) in 150 cc methanol under nitrogen was treated at 0° with stirring with a solution of 2·25 g potassium hydroxide in 2·5 cc water and 50 cc methanol. The reaction mixture was allowed to stand at room temp for 1·5 hr followed by neutralization with 2·5 cc acetic acid and evaporation *in vacuo* to an oil. The oil was extracted with ethyl acetate and crystallized from this solvent to give 3·63 g first crop of the triol II (R = H), m.p. 202–205°.

(Found: C, 68·98; H, 8·54. Calc. for $C_{21}H_{32}O_5$: C, 69·23; H, 8·79%).

In a similar fashion 448 mg of the ketol diacetate III (R = Ac) was saponified in the cold to give 350 mg of the corresponding triol III (R = H), m.p. 167–169°.

(Found: C, 68·89; H, 9·09. Calc. for $C_{21}H_{32}O_5$: C, 69·23; H, 8·79%).

3α, 17-Dihydroxy Δ^{14}*-5β-D-homoandrostene-11,17a-dione* (V) (R = H)

A solution of 2·5 g of the triol II (R = H) in 130 cc methanol was treated with 1·47 g sodium metaperiodate in 50 cc water. After 5 hr the reaction mixture was filtered from precipitated sodium iodate and evaporated to near dryness. The residue was dissolved in 5–10% KOH_{aq}, filtered and the filtrate acidified. The precipitated product was dissolved in ethyl acetate and the ethyl acetate extract washed several times with potassium bicarbonate solution. Acidification of the potassium bicarbonate extracts precipitated a small amount of the crystalline acid XVI, m.p. 249–253° (see below). The ethyl acetate layer was dried, and evaporated and the residue crystallized from acetone–ether to give 1·7 g of the diosphenol V (R = H), m.p. 211–215°; λ_{max} 267 mμ, E = 16,200.

(Found: C, 72·22; H, 8·22. Calc. for $C_{20}H_{28}O_4$: C, 72·29; H, 8·43%).

Acetylation of V (R = H) with acetic anhydride in pyridine afforded the *3,17-diacetate* V (R = Ac), m.p. 211–215°; λ_{max} 233 mμ, E = 7,500.

(Found: C, 68·94; H, 7·74. Calc. for $C_{24}H_{32}O_6$: C, 69·23; H, 7·69%).

In a similar fashion 300 mg of the ketol III in 20 cc methanol was cleaved with 176 mg sodium metaperiodate in 8 cc water to give the diosphenol V identical with material obtained from II above.

Oxidation of diosphenol 3,17-diacetate (V, R = Ac) *to 3α-acetoxy-11-keto-etiobilianic acid* (X)

A solution of 100 mg V (R = Ac) in 10 cc acetone was oxidized according to published procedure[2] with 130 mg $KMnO_4$ for 3–4 hr. The oxidation product was worked up in the usual manner and afforded the etiobilianic acid X m.p. 225–230° undepressed on mixed m.p. with an authentic sample.

[15] Melting points were taken on a micro hot-stage apparatus and are corrected. U.V. spectra were determined in methanol and rotation in chloroform.

3α-17-Dihydroxy 5β-D-homoandrostane-11, 17a-dione or 3α, 17a-dihydroxy 5β-D-homoandrostane-11, 17-dione (VIII or IX)

A solution of 1·38 g 3α-acetoxy 5β-D-homoandrostane-11, 17a-dione[3] in 30 cc chloroform was treated with 0·69 g bromine in 10 cc chloroform. A drop of 15% hydrogen bromide in acetic acid was employed as catalyst. The bromination product was dissolved in 50 cc tetrahydrofuran and refluxed for 1 hr with a solution of 1 g potassium hydroxide in 50 cc water. Concentration of the reaction mixture caused deposition of the product as a solid. The latter was separated and crystallized from acetone–ether, m.p. 224–230°, wt. 800 mg.

(Found: C, 71·99; H, 8·85. Calc. for $C_{20}H_{30}O_5$: C, 71·85; H, 8·98%).

VOL. 7 1959

Oxidation of the ketol VIII *or* IX *to the diosphenol* (V)

A solution of 50 mg of the ketol (VIII or IX) in 4 cc methanol was treated with 75 mg copper acetate monohydrate and refluxed for 1 hr. Separation of cuprous oxide was evident after several min. The reaction mixture was worked up by addition of 0·5 cc water followed by refluxing for 0·5 hr followed by filtration and evaporation of the filtrate *in vacuo*. The residue was acetylated with acetic anhydride in pyridine and the acetylated product crystallized from ether, m.p. 206–211°. Mixed m.p. with diosphenol diacetate (V, R = Ac) prepared by periodate cleavage of II or III (R = H) above was 208–214°. The infrared spectra of the two samples were the same.

3α-17-*Dihydroxy*-16-*methyl*-Δ^{16}-5β-D-*homoandrostene*-11,17a-*dione* (IV)

(A) A solution of 3·65 g of the 17a-ketone diacetate II (R = Ac) in 150 cc methanol was treated with 30 g potassium hydroxide in 30 cc water and 150 cc methanol. The alkali was added to the steroid from a dropping funnel in a nitrogen atmosphere and the reaction mixture refluxed for 15–18 hr. At the end of this period the reaction mixture was cooled and acidified with 50 cc conc HCl diluted with an equal volume of water. The solvents were evaporated *in vacuo* and the residue dissolved in 10% KOH_{aq}, filtered, acidified and the precipitated product extracted with ethyl acetate. The ethyl acetate extract on washing with potassium bicarbonate solution afforded, after acidification, 300 mg of the 16β-methyl 17-isoetianic acid (XX) (see below). The washed ethyl acetate layer was dried and evaporated to the point of crystallization whereby 2·31 g of the methyl diosphenol (IV) was afforded; m.p. 238–243°, λ_{max} 273 mμ, E = 8600.

(Found: C, 72·80; H, 8·70. Calc. for $C_{23}H_{34}O_4$: C, 72·83; H, 8·67%).

(B) In an identical manner and in equal yield the methyl diosphenol IV was prepared from the ketolic isomer III (R = Ac).

Acetylation of IV (R = H) with acetic anhydride in pyridine afforded the 3,17-*diacetate* (IV, R = Ac), m.p. 220–222°, λ_{max} 239 mμ, E = 10,850.

(Found: C, 69·93; H, 7·96. Calc. for $C_{25}H_{34}O_6$: C, 69·77; H, 7·91%).

Oxidation of the methyl diosphenol diacetate (IV, R = Ac) *and* 3α-*acetoxy*-16-*methyl*-Δ^{16}-*pregnene*-11, 20-*dione* XII *to the methyl ketonic acid* (XI)

(A) A solution of 500 mg IV (R = Ac) in 50 cc acetone at 0° was treated with 650 mg potassium permanganate and allowed to stir at room temp for 2 hr. At the end of this time the acetone was evaporated in a stream of nitrogen and replaced with water; the latter was acidified with 7·5 cc 50% H_2SO_4 and decolorized with saturated sodium bisulfite solution. The product was taken up in ether and the organic acid extracted with bicarbonate, released from the latter by acidification and re-extracted with ether. Evaporation of the dried ether solution gave a non-crystalline acid XI identical in the infrared spectrum with the acid obtained from XII on oxidation (see Part B below). This acid gave a copious precipitate of iodoform, m.p. 120–121°, on treatment with sodium hypoiodite solution to form X.

(B) Similar oxidation of the Δ^{16}-*pregnene derivative* XII[3] gave the same amorphous acid XI identical by infrared spectral comparison with the sample obtained from IV (R = Ac) *Part A*.

D-*Homoannulation of* 3α, 21-*diacetoxy*-17α-*hydroxy* 16β-*methyl pregnane* 11,20-*dione* (XIII)

A solution of 900 mg XIII[4] in 10 cc dioxane and 30 cc toluene was treated with 6 cc cyclohexanone and 200 mg aluminum isopropoxide and the reaction mixture refluxed for 2·5 hr. The product was

worked up in the same manner described for the preparation of II and III (see above). The D-homo compound (XIV, R = Ac) crystallized directly from acetone–ether to give a first crop of 500 mg m.p. 191–193°.

(Found: C, 67·22; H, 8·10. Calc. for $C_{23}H_{36}O_7$: C, 67·53; H, 8·44%).

Conversion of D-*homo compound* XIV *to methyl diosphenol* (IV)

A solution of 400 mg XIV (R = Ac) in 15 cc methanol was hydrolyzed to XIV (R = H) with 194 mg potassium hydroxide at room temp for 1·5 hr. The reaction product was isolated by neutralization with acetic acid and extraction with ethyl acetate. The residue (200 mg) obtained on evaporation of the solvent was dissolved in 10 cc methanol and treated with 119 mg sodium metaperiodate. The product from the cleavage reaction was worked up in the same manner as described for the preparation of V(R = H) and afforded the methyl diosphenol (IV, R = H) identical in m.p. and infrared spectrum with that obtained from the alkaline rearrangement of II and III (see above). Acetylation of this material afforded 3, 17 *diacetate* identical with (IV, R = Ac) obtained previously, m.p. and mixed m.p. 217–221°. The infrared spectra of the two samples were the same.

Synthesis of methyl diosphenol IV *by hydroxymethylation of the ketol* (VIII or IX)

A solution of 150 mg of the ketol (VIII or IX) in 10 cc methanol containing 300 mg potassium hydroxide dissolved in 1 cc water was treated dropwise under reflux and a nitrogen atmosphere with 0·04 cc 37% formaldehyde solution dissolved in 2 cc methanol. The reaction mixture was refluxed a total of 1·5 hr. At the end of this period the base was neutralized with acetic acid and the solvents evaporated *in vacuo*. The residue was dissolved in ethyl acetate and the ethyl acetate extract washed with bicarbonate, dried and concentrated to dryness. The residue was acetylated with acetic anhydride in pyridine for 15 hr at room temp and the acetylated product chromatographed on acid-washed alumina. The fractions eluted with 2–10% ether in benzene gave the methyl diosphenol diacetate (IV, R = Ac) m.p. 218–220°, mixed m.p. with IV (R = Ac) prepared from the alkaline rearrangement of the ketols II and III was not depressed (218–220°). The infrared spectra of the two samples were identical.

3α,17β-*Dihydroxy*-11-*keto* 17-*isoetianic acid* (XVII)

A solution of 200 mg of the diosphenol V (R = H) in 20 cc methanol was treated with 3 g potassium hydroxide in 3 cc water and refluxed in a nitrogen atmosphere for 15 hr. The reaction mixture was concentrated to dryness and the organic material extracted with ethyl acetate. The ethyl acetate solution was extracted with potassium bicarbonate solution and the latter on acidification deposited 210 mg crystalline acid XVII. The acid was recrystallized from acetone, m.p. 252–254° (dec).

Found: C, 68·66; H, 8·59. Calc. for $C_{20}H_{30}O_5$: C, 68·54; H, 8·63%).

The acid XVII was different from the known etianic acid XVIII and was converted to the 17-ketone XIX as follows: a 500 mg sample of XVII was esterified with diazomethane and acetylated with acetic anhydride in pyridine. The total esterified and acetylated product was dissolved in 25 cc methanol and cleaved with 600 mg sodium metaperiodate dissolved in 12 cc water for 15 hr. The cleavage product, 3α, 11β-*dihydroxy* 5β-*androstane*-11-*one* (XIX) crystallized from the concentrated reaction product, was filtered and recrystallized from acetone, m.p. 233–236°.

(Found: C, 74·30; H, 9·86. Calc. for $C_{19}H_{30}O_3$: C, 74·51; H, 9·80%).

The above sample of XIX prepared from XVII was identical with a specimen prepared from 3α, 17α-dihydroxy-11-keto etianic acid (XVIII) by the same route. The intermediate *methyl* 3α-*acetoxy*-17α-*hydroxy*-11-*keto etianate* melted at 140–142°.

(Found: C, 67·83; H, 8·27. Calc. for $C_{23}H_{34}O_6$: C, 67·98; H, 8·37%).

3α,17β-*Dihydroxy*-11-*keto*-16β-*methyl* 17-*isoetianic acid* (XX)

(A) A solution of 500 mg methyl diosphenol IV (R = H) dissolved in 25 cc methanol containing 6 g potassium hydroxide in 5 cc water was refluxed 18 hr in a nitrogen atmosphere. Concentration of the reaction mixture and dilution with water deposited 450 mg crystalline acid XX recrystallized from acetone, m.p. 277–280°.

(Found: C, 68·98; H, 8·75. Calc. for $C_{21}H_{32}O_5$: C, 69·23; H, 8·79%).

(B) A solution of 1·58 g of the ketol II (R = Ac) in 50 cc methanol containing 12 g potassium hydroxide in 12 cc water was refluxed in a nitrogen atmosphere for 15 hr. The work-up of the product afforded 400 mg methyl diosphenol IV (R = H) and the bicarbonate soluble fraction afforded 1·05 g crystalline acid XX.

Conversion of 3α,17β-*dihydroxy*-11-*keto*-16β-*methyl*-17-*isoetianic acid* XX *to* 3α-*acetoxy*-16β-*methyl*-5β-*androstane*-11,17-*dione* (XXI)

A 200 mg sample of XX was esterified in methanol solution with diazomethane followed by acetylation at C-3 with acetic anhydride in pyridine in the usual manner. The ester acetate was reduced with 500 mg lithium aluminum hydride in 50 cc refluxing tetrahydrofuran and the product cleaved in methanol with 2 equivalents of sodium metaperiodate to afford 3α,11β-*dihydroxy*-16β-*methyl* 5β-*androstane*-17-*one* (XXIa). The latter was crystallized as plates from acetone–ether, m.p. 186–188°.

(Found: C, 75·3; H, 10·1. Calc. for $C_{20}H_{32}O_3$: C, 75·0; H, 10·0%).

A sample of the above 17-ketone (XXIa) was acetylated with acetic anhydride in pyridine and oxidized at C-11 with chromic acid in acetic acid to give 3α-acetoxy-16β-methyl-5β-androstane-11, 17-dione (XXI) as prisms from ether, m.p. 202–205°. This material was identical by mixed m.p. and infrared comparison with a sample of XXI prepared by methylation of 3α-acetoxy-5β-androstane-11,17-dione (see below).

3α-*Acetoxy* 16-*methylene* 5β-*androstane*-11,17-*dione* (XXIV)

A 3·46 g sample of 3α-acetoxy-5β-androstane-11,17-dione in 25 cc isoamyl alcohol was treated with 1·5 g paraformaldehyde and 6·1 g dimethylamine hydrochloride and heated under reflux for 2 hr.[12] After standing overnight in the ice box the reaction mixture was treated with 40 cc 1:9 conc HCl–water and extracted with ether. The aqueous layer was treated with saturated sodium carbonate solution and extracted with ether. The residue obtained after evaporation of the ether was steam distilled and the residue from the steam distillation was crystallized from acetone–ether to give XXIV, m.p. 234–239°, λ_{max} 228 mμ, E = 8,800.

(Found: C, 73·36; H, 8·38. Calc. for $C_{22}H_{30}O_4$: C, 73·74; H, 8·41%).

Hydrogenation of 3α-*acetoxy*-16-*methylene*-5β-*androstane* 11,17-*dione* (XXIV to XXI)

A 100 mg sample of XXIV in 25 cc methanol and 50 mg 50% palladium on charcoal was hydrogenated. Uptake of 1 mole of hydrogen was complete in 3–4 min. The product was filtered, evaporated and crystallized from acetone–ether, m.p. 202–205°. A mixed m.p. of XXI obtained by the above route was undepressed on admixture with a sample prepared from degradation of the acid XX and the ketol XXII (see below). The infrared spectra of these samples were identical.

Reductive cleavage of 3α,17α-*dihydroxy*-16β-*methyl*-*pregnane*-11, 20-*dione* (XXII *to* XXI)

To a stirred solution of 2·00 g of the diol-dione XXII in 60 ml tetrahydrofuran was added 1·00 g sodium borohydride in 10 ml water and the mixture refluxed for 50 min. It was then cooled and the remaining reducing agent destroyed by addition of dilute acetic acid. Following concentration on the water pump, water was added and the mixture extracted with ethyl acetate. To the residue (1·97 g mainly 3α,17α,20-*trihydroxy*-16β-*methylpregnane*-11-*one*) in 60 ml methanol was added 2·00 g sodium metaperiodate in 25 ml water with stirring and cooling. After 18 hr at 25° the precipitated sodium iodate was removed by filtration and washed with ethyl acetate. Water was added to the filtrate which was then concentrated on the water pump until the organic solvents were removed and the product had precipitated. The crystalline product, 3α-*hydroxy*-16β-*methyl*-5β-*androstane*-11, 17-*dione*[16] was washed with water and dried in air; 1·32 g m.p. 235–245° raised to 242–250° on crystallization from acetone λ_{max}^{Nujol} 2·86, 2·89 μ (OH); 5·78 μ (17 C=O); 5·86 μ (11 C=O).

Acetylation at 25° in acetic anhydride–pyridine gave 3α-acetoxy-16β-methyl-5β-androstane-11 17-dione (XXI) prismatic needles from ether m.p. 203–206°.

(Found: C, 73·26; H, 8·82. Calc. for $C_{22}H_{32}O_4$: C, 73·30; H, 8·95%).

[16] It is noteworthy that under the above reduction conditions which suffice to completely reduce the 11-keto group in the pregnane series, the 11-keto group in the 16β-methyl-pregnane series remains essentially unchanged. Only a few mg of crude 3α,11β-dihydroxy-16β-methyl-5β-androstane-17-one XXIa were obtained by extraction of the aqueous mother liquors and fractional crystallization.

VOL. 7 1959

Lithium aluminum hydride reduction of XXII in refluxing anhydrous tetrahydrofuran followed by periodate cleavage gave 3α,11β-dihydroxy-16β-methyl-5β-androstane-17-one XXIa, m.p. 187–188° identical with material obtained from the isoetianic acid XX by melting point and infrared spectral comparisons.

3α-17β-Dihydroxy-11-keto-16, 16-bis-hydroxymethyl-17-isoetianic acid lactone (XVII)

A solution of 350 mg of the diosphenol (V) in 10 cc isopropanol containing 0·5 g potassium hydroxide and 1 cc formaldehyde (37%) was refluxed for 2 hr. After 15–20 min of reflux two layers formed. At the conclusion of the reflux period the reaction mixture was acidified and concentrated *in vacuo*. The residue was dissolved in 5% KOH and upon acidification there was a delayed precipitation of the product. The latter was extracted with ethyl acetate and the ethyl acetate layer washed several times with potassium bicarbonate solution. Evaporation of the dried ethyl acetate solution induced crystallization of the lactone XVII, m.p. 270–273°, wt. 300 mg, λ_{max}^{Nujol} 2·8, 3·0 and 3·14 μ (OH), 5·68 μ (5-ring lactone) and 5·86 μ (11C=O).

(Found: C, 67·37; H, 8·21. Calc. for $C_{22}H_{32}O_6$: C, 67·35; H, 8·16%).

A 200 mg sample of the lactone (XVII) was reduced in refluxing tetrahydrofuran with 1 g lithium aluminum hydride followed by cleavage of the reduced product with sodium metaperiodate. The non-crystalline oxidation product exhibited in the infrared in addition to OH absorption a band at 5·79 μ.

3α,17β-Dihydroxy-11-keto-16β-methyl-16α-hydroxymethyl-17-isoetianic acid lactone (XVIII)

A 200 mg sample of the methyl diosphenol (IV) in 10 cc methanol containing 0·5 g potassium hydroxide in 1 cc water and 1 cc 37% formaldehyde solution was refluxed for 2 hr. The product was worked up as in the preparation of XVII to give 100 mg lactone XVIII from ethyl acetate, m.p. 257–259°, λ_{max}^{Nujol} 2·8–2·95 and 3·12 μ (OH), 5·69 μ (5-ring lactone) 5·95 μ (11 C=O); λ_{max}^{Chf} 2·83 μ (OH), 5·69 μ (5-ring C=O), 5·84 μ (11C=O).

(Found: C, 70·24; H, 8·44. Calc. for $C_{22}H_{32}O_6$: C, 70·21; H, 8·51%).

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VOL.
7
1959

EXTENSION OF BISCHLER–NAPIERALSKI REACTION—IV*

SYNTHESIS OF SOME PYRIDINE DERIVATIVES

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Abstract—Acyl derivatives of 5-phenylpent-4-enylamine were cyclized to give 2-substituted 3-benzal-3,4,5,6-tetrahydropyridines in good yield. This is a new synthesis of pyridine derivatives.

THE new synthesis of pyridine derivatives involves the cyclization of acyl derivatives of 5-phenyl-pent-4-enylamine (II)[1] under the usual conditions of Bischler–Napieralski reaction, giving good yields of 2-R-3-benzal-3,4,5,6-tetrahydropyridines (cf. IVa and IVb). Catalytic reduction of the metho salt of IVa gives 1-methyl-2-phenyl-3-benzylpiperidine (V), the methochloride of which was submitted to the modified Emde degradation[2] yielding N,N-dimethyl-4,4-dibenzyl-n-butylamine (VI), and the methochloride of the latter on exhaustive methylation gave 4,4-dibenzyl-but-1-ene (VII), in which the presence of an end vinyl group was revealed by I.R. spectra. On oxidation VII gave a mixture of acids which was converted into anilide and separated chromatographically, and only pure dibenzylacetanilide (VIII) was obtained indicating the point of cyclization of III. An impure anilide was isolated from the second eluate of the chromatographical analysis which was probably β,β-dibenzylpropionanilide (IX) which melted over a range 108–130°; an authentic specimen of IX (m.p. 126–127°) was prepared from β,β-dibenzylpropionic acid synthesized by the Arndt–Eistert method. VI was synthesized from 4,4-bibenzylbutyramide (X) which was reduced by $LiAlH_4$ to 4,4-dibenzylbutylamine (XI) which was methylated by the Eschweiler method to yield VI identical with the base obtained previously. All evidence indicates the six-membered ring nature of the cyclized base. The location of the double bond was deduced from analogy of the previous investigation,[1] and also from a strong bathochromic shift of the maxima of the U.V. spectrum of IVa by comparison with IIIa.

Dehydrogenation of IVa (Pd. C) gave 2-phenyl-3-benzyl-pyridine, and on similar treatment IVb gave a product which was not identified. 2-Methyl-3-benzylpiperidine, the reduced product from IVb, was dehydrogenated to 2-methyl-3-benzylpyridine, which on oxidation gave 3-benzoylpicolinic acid identical with the same product previously obtained.[3] The structure of IVb and its reduced product 2-methyl-3-benzylpiperidine are confirmed.

The formylderivative of II did not give 3-benzal-3,4,5,6-tetrahydropyridine (XII) but the carbethoxyformyl derivative (XIII) of II yielded XIV.

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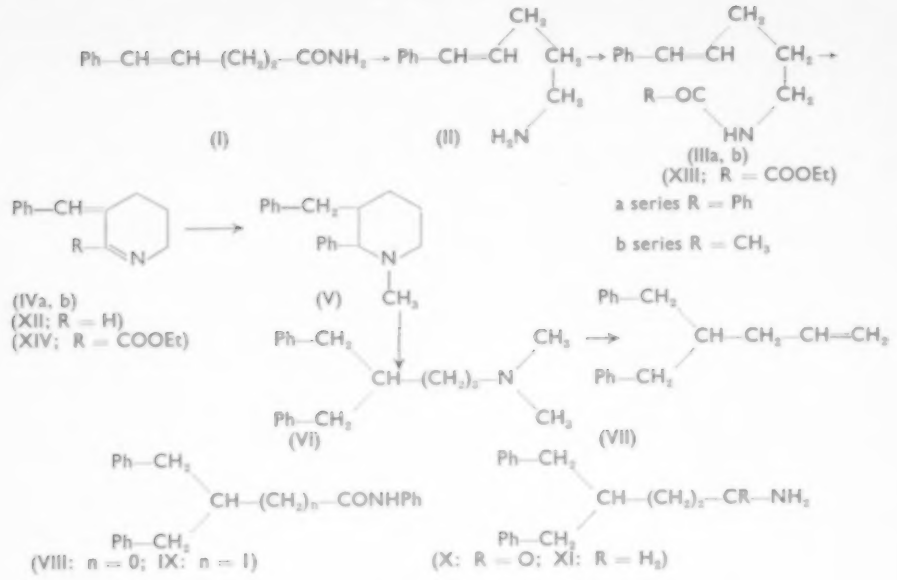

EXPERIMENTAL

5-Phenylpent-4-enoylamide (I). Crude 5-penylpent-4-enoyl chloride was added dropwise to excess conc ammonia at 0° with stirring. A quantitative yield of the *amide* (I) was obtained as colourless needles from benzene m.p. 133–134°, (Found: C, 75·3; H, 7·6; N, 8·0. $C_{11}H_{13}ON$ requires: C, 75·4; H, 7·5; N, 8·0%).

5-Phenylpent-4-enylamine (II). Lithium aluminium hydride (17·5 g) was suspended in a mixture of anhydrous ether (100 ml) and dioxan (130 ml) and to this mixture a solution of I (40 g) dissolved in dioxan (350 ml) was added with stirring at 10°. After additional stirring for 12 hr at room temp the mixture was heated at 50° for 1 hr, and the product worked up as usual. A colourless oil b.p. 111° (3 mm) was obtained (29·4 g, 80%) from which the following crystalline derivatives were prepared.

Hydrochloride. Colourless rhombs m.p. 180° (decomp) from ether–ethanol, (Found C, 66·9; H, 8·2; N, 7·0. $C_{11}H_{16}NCl$ requires: C, 66·8; H, 8·15; N, 7·1%).

Picrate. Yellow needles m.p. 157–158° from ethanol–diisopropylether, (Found C, 52·1; H, 4·8; N, 14·6. $C_{17}H_{18}O_7N_4$ requires: C, 52·3; H, 4·65; N, 14·35%).

N-(5-Phenylpent-4-enyl)-benzamide (IIIa). This was obtained in almost quantitative yield from II by benzoylation. The product separated in colourless feathers m.p. 63–64° when crystallized from a mixture of benzene and ligroin (b.p. 80–120°), (Found C, 81·6; H, 7·1:, N, 5·0. $C_{18}H_{19}ON$ requires: C, 81·5; H, 7·2; N, 5·3%) U.V. λ_{max}^{EtOH} 252, 283, 293 mμ, (log ε 4·42, 2·37, 2·20).

N-(5-Phenylpent-4-enyl)-acetamide (IIIb). II was acetylated with acetic anhydride yielding IIIb almost quantitatively as colourless feathers m.p. 65–66° crystallizing from a mixture of benzene and petroleum ether. (b.p. 45–80°) (Found C, 76·5; H, 8·45; N, 7·0. $C_{13}H_{17}ON$ requires: C, 76·8; H, 8·4; N, 6·9%).

N-(5-Phenylpent-4-enyl)-formamide. II (0·8 g) was heated with ethyl formate (0·5 g). The product (0·92 g, 98%) was crystallized from petroleum ether (b.p. 45–80°) in colourless scales m.p. 59·5–60·5°. (Found: C, 76·3; H, 7·9; N, 7·65. $C_{12}H_{15}ON$ requires: C, 76·15; H, 8·0; N, 7·4%).

N-(5-Phenylpent-4-enyl)-ethoxycarbonylformamide (XIII). To a mixture of II (2·85 g), ether (50 ml), $KHCO_3$ (8 g) and water (20 ml) was added ethoxycarbonylformyl chloride (3 g) dropwise at 0° with stirring. After stirring for 1 hr the product (4·27 g, 92%) crystallized in colourless needles m.p. 62–64° from n-hexane, (Found: C, 68·9; H, 7·4; N, 5·4. $C_{15}H_{19}O_3N$ requires: C, 68·9; H, 7·3; N, 5·4%).

2-Phenyl-3-benzal-3,4,5,6-tetrahydropyridine (IVa). A mixture of IIIa (9·0 g), phosphoryl chloride (37 ml) and benzene (54 ml) was refluxed for about 4 hr. On working up the reaction product IVa

was obtained (6·52 g, 77·5%) and crystallized from petroleum ether (b.p. 45–80°), colourless rhombs, m.p. 70–71°. (Found: C, 87·5; H, 6·7; N, 5·9. $C_{16}H_{17}N$ requires: C, 87·4; H, 6·9; N, 5·7%). U.V. λ_{max}^{EtOH} 286 mμ (log ε 4·33).

The *picrate* formed yellow rhombs from ethanol m.p. 183–184°, (Found: C, 60·6; H, 4·25; N, 11·7. $C_{24}H_{20}O_7N_4$ requires: C, 60·5; H, 4·2; N, 11·8%).

The *methiodide* separated in yellow needles m.p. 193–194° from a mixture of ether and methanol. (Found: C, 58·7; H, 5·3; N, 3·5. $C_{19}H_{20}NI$ requires: C, 58·6, H, 5·2; N, 3·6%).

2-*Methyl*-3-*benzal*-3,4,5,6-*tetrahydropyridine* (IVb). A mixture of IIIb (2 g), phosphoryl chloride (9 ml) and benzene (12 ml) gave after being refluxed for 1·5 hr a yellowish red oily base (1·81 g). The crude base was dissolved in benzene and purified through an alumina column. The pale yellow oil (IVb, 1·3 g, 71·2%) was characterized as the *picrate*, which formed yellow plates m.p. 187–188° from methanol, (Found: C, 55·1; H, 4·4; N, 13·5. $C_{19}H_{15}O_7N_4$ requires: C, 55·45; H, 4·4; N, 13·9%).

2-*Ethoxycarbonyl*-3-*benzal*-3,4,5,6-*tetrahydropyridine* (XIV). A mixture of XIII (0·62 g), phosphoryl chloride (2·7 cc) and benzene (2·7 cc) was refluxed for 30 min to give XIV (0·21 g, 36%). The *picrate* formed yellow needles m.p. 152–153° from ethanol, (Found: C, 53·2; H, 4·3; N, 12·0. $C_{21}H_{20}O_9N_4$ requires: C, 53·4; H, 4·3; N, 11·9). The *methiodide* crystallized in yellow needles m.p. 126° (decomp) from methanol–ether, (Found: C, 49·6; H, 5·0; N, 3·5. $C_{16}H_{20}O_2NI$ requires: C, 49·9; H, 5·2; N, 3·6).

2-*Phenyl*-3-*benzyl*-1-*methylpiperidine* (V). The methiodide (4 g) of IV was converted into the corresponding chloride and was reduced over Adams Pt-catalyst in ethanol. (ca. 2 molar equivalents of H_2 being absorbed). The product (V) was a colourless oily base b.p. 145–146° (2 mm) (2·32 g, 85·2%). U.V. λ_{max}^{EtOH} 259 mμ (log ε 2·73). The *picrate* formed yellow needles m.p. 190–191° from ethanol, (Found: C, 61·0; H, 5·5; N, 11·45. $C_{25}H_{26}O_7N_4$ requires: C, 60·7; H, 5·3; N, 11·3).

N,N-*Dimethyl*-4,4-*dibenzyl*-*n*-*butylamine* (VI).

(i) A mixture of V (2·32 g), methyl iodide (5 ml) and methanol (6 ml) was refluxed to form the methiodide of V which was directly converted into methochloride. The latter was dissolved in aq. NaOH (70 ml, 20%) to which powdered Raney nickel alloy (2 g) was added gradually with stirring. After addition of the alloy the mixture was stirred at 30° for 4 hr and then extracted with benzene, dried and the solvent removed. The residue distilled at 152–154° (1·5 mm) as a colourless oil (2·3 g, 93%), (Found: C, 85·5; H, 9·9; N, 5·3. $C_{20}H_{27}N$ requires: C, 85·35; H, 9·7; N, 5·0%). The *picrate*, yellow plates m.p. 101–102° from ethanol, (Found: C, 61·2; H, 6·0; N, 11·1. $C_{20}H_{30}O_7N_4$ requires: C, 61·2; H, 5·9; N, 11·0%). The *methiodide* separated as colourless scales from methanol–ether m.p. 144–145°, (Found: C, 59·75; H, 7·4; N, 3·9; I, 30·3. $C_{21}H_{30}NI$ requires: C, 59·6; H, 7·1; N, 3·3; I, 30·0%).

(ii) Dibenzylacetyl chloride was converted by the Arndt–Eistert method into the diazoketone, pale yellow needles from n-hexane m.p. 77–77·5° (84%), (Found: C, 77·3; H, 6·3. $C_{17}H_{16}ON_2$ requires: C, 77·25; H, 6·1%). The diazoketone (1·4 g) in ethanol (15 ml) and a small amount of silver oxide was warmed at 55° until evolution of gas had ceased (15 min). Active charcoal powder was added and the mixture was filtered and the solvent removed leaving a residue of ethyl 3,3-dibenzylpropionate, which was hydrolysed yielding 3,3-dibenzylpropionic acid, colourless prisms m.p. 84–85·5° from petroleum ether, (Found C, 80·5; H, 6·95. $C_{17}H_{18}O_2$ requires: C, 80·3; H, 7·1%).

4,4-*Dibenzylbutyramide* (X). 3,3-Dibenzylpropionyl chloride (b.p. 162°, 0·12 mm) (0·91 g) was treated with diazomethane (from nitrosomethylurea 1·8 g) and the crude diazoketone was added to a mixture of dioxan (5 ml) and conc ammonia (7·5 ml) and to the solution silver nitrate (2 ml, 10%) was added dropwise. The evolution of nitrogen ceased after ½ hr at 70° and the amide was dissolved in benzene, washed and dried and the solvent evaporated. The amide was dissolved in benzene and purified through an alumina column, and crystallized from a mixture of n-hexane and benzene in colourless needles m.p. 88–89° (0·69 g, 65%), (Found: C, 81·1; H, 8·0: N, 5·3. $C_{18}H_{21}ON$ requires: C, 80·9; H, 7·9: N, 5·2%).

4,4-*Dibenzylbutylamine* (XI). The amide (0·5 g) in ether (20 ml) and dioxan (20 ml) was added dropwise to $LiAlH_4$ (0·15 g) in ether (10 ml), and the mixture refluxed for 6 hr. On working up, the product distilled at 178–180° (3 mm) as a colourless oil (0·32 g, 67·5%). The *picrate*, yellow plates m.p. 135–136° crystallized from ethanol and diisopropylether, (Found C, 59·8; H, 5·7; N, 11·9. $C_{24}H_{26}O_7N_4$ requires: C, 59·7; H, 5·4; N, 11·6%). The *amine* XI (0·25 g) dissolved in formic acid

(0·3 g, 85%) and aqueous formaldehyde solution (0·3 ml, 35%) was heated at 100° for 2·5 hr. The *base* (VI) was obtained as an oil (0·215 g, 77·3%), b.p. 180° (2 mm). The *picrate* crystallized in yellow needles m.p. 101–103° from ethanol, and the *methiodide*, colourless scales m.p. 144–145° from methanol–ether were found to be identical with those from V described previously.

For exhaustive methylation, the methiodide (2·05 g) was triturated with methanol and freshly prepared silver oxide, filtered and the residue submitted to distillation *in vacuo* which yielded an oil (b.p. 160°, 2 mm) consisting of a basic fraction soluble in HCl and a neutral fraction (0·19 g, 16·6%) which was 4,4-dibenzylbut-1-ene (VII) b.p. 140° (2 mm). U.V. λ_{max}^{EtOH} 259 mμ (log ε 2·76). I.R. (C=C) 1642 cm^{-1} 996, 912 cm^{-1} (—CH=CH_2). The basic fraction was VI identified as the *methiodide*.

A solution of potassium permanganate (0·34 g) in acetone (35 ml) was added dropwise to a solution of VII (0·175 g) in acetone (7 ml) at room temp. The product (0·11 g) could not be crystallized and was converted to the anilide (0·08 g) m.p. 110–112° which was purified through an alumina column using a mixture of benzene and n-hexane. The first fraction yielded colourless needles of dibenzylacetanilide m.p. 156–157°, (Found: C, 83·8; H, 6·8; N, 4·5. $C_{22}H_{21}$ ON requires: C, 83·8; H, 6·7; N, 4·4). A second fraction yielded a solid m.p. 108–130° from which nothing definite could be isolated; it probably contained the anilide of β,β-dibenzylpropionic acid, an authentic specimen of which was prepared, m.p. 126–127°, (Found: C, 84·2; H, 7·15; N, 3·9. $C_{23}H_{23}ON$ requires: C, 83·85; H, 7·0; N, 4·25%).

2-*Phenyl*-3-*benzylpyridine*. A mixture of IVa (0·2 g), 30% Pd—C (50 mg) and ethyl cinnamate (4 ml) was refluxed in an atmosphere of nitrogen for 1 hr. On cooling, the product was extracted with dilute HCl and the acid solution was basified to separate an oily base, which was collected in benzene, washed, dried, and the solvent removed. The yellowish oil (0·14 g, 70·5%) was characterized as the *picrate*, yellow plates from methanol m.p. 157–158°, (Found: C, 60·6; H, 3·9; N, 11·9. $C_{24}H_{18}O_7N_4$ requires: C, 60·8; H, 3·8; N, 11·8%). The *base* recovered from the picrate formed a colourless syrup, b.p. 215–220° (2 mm). U.V. λ_{max}^{EtOH} 272 mμ (log ε 3·65).

2-*Methyl*-3-*benzylpyridine*. IVb (1·36 g) in ethanol (40 ml), acidified by adding conc HCl (2 ml), was reduced catalytically over Adams Pt-catalyst, 2 molar equivalents of H_2 being absorbed. 2-*Methyl*-3-*benzylpiperidine* distilled at 109–110° (2 mm) yielding colourless oil (0·68 g). U.V. λ_{max}^{EtOH} 259 mμ (log ε 2·38). This (0·2 g) was dehydrogenated and a yellowish oil was obtained which was characterized as the *picrate*, yellow needles from methanol, m.p. 148–150°, (Found: C, 55·55; H, 4·0; N, 13·6. $C_{19}H_{14}O_7N_4$ requires: C, 55·3; H, 3·9; N, 13·6%). The *base* recovered from the picrate was a colourless oil, b.p. 130° (2 mm). UV λ_{max}^{EtOH} 265 mμ (log ε 3·62).

3-*Benzoylpicolinic acid*. The foregoing base (0·11 g) was warmed (steam-bath) and oxidized by adding aq. solution of potassium permanganate until no more decolourization was observed. The filtrate from MnO_2 was concentrated to a small volume, acidified by HCl and mixed with aq. cupric acetate to precipitate blue copper salt of the acid, which was collected and decomposed with H_2S. From the filtrate 0·1 g of the acid was obtained, which formed colourless prisms from water, m.p. 147° (decomp). An authentic specimen also melted and decomposed at the same temp. and their identity was also established beyond doubt by comparing their I.R. spectra.

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VOL.
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REACTIONS OF IONS WITH MOLECULES IN THE GAS PHASE

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Abstract—Existing knowledge concerning the gas phase reactions of ions with molecules is summarized in terms of the identification of the reactions, the rate constants of the reactions, and the energetic properties of the ions observed to be formed and of those inferred as intermediates.

INTRODUCTION

IN the last few years considerable attention has been given to a newly recognized type of chemical reaction, namely, gas-phase reaction between ions and molecules. Although it has been recognized for a long time that such reactions were possibly of considerable importance in many gas-phase processes such as radiation chemistry, electric discharges, flames, etc., little or no detailed knowledge of the reactions existed. The constant improvement in mass spectrometric instrumentation and technique, while permitting the compilation of a large amount of useful information concerning the properties of isolated gaseous ions,[1] caused a neglect of the study of the reactions that take place upon collision of the ions with molecules. Secondary reactions between ions and molecules were observed by early workers in mass spectrometry[2] but were treated, for the most part, as nuisances due to experimental difficulties. The existence of such reactions also was recognized theoretically many years ago, as evidenced by the calculations on the rate of formation of H_3^+ in ionized hydrogen, by Eyring *et al.*[3] However, it was not until about 1952 that papers directly concerned with the experimental study of these secondary reactions began to appear in the literature. Such mass spectrometric investigations are of considerable general interest to chemists because they afford the opportunity of obtaining information not only on the energetics and unimolecular decomposition reactions of isolated ions but also on the bimolecular reactions of the ions with normal molecules. It goes without saying that such information is of value to persons working with systems in which ions are involved, a classification which includes those interested in both physical and organic chemistry.

Gaseous ions are high-energy transient entities and it is therefore not surprising that all direct observations of their reactions (both unimolecular and bimolecular) have been made in instruments designed to separate and detect such electrically charged molecular species, namely, in mass spectrometers. In the last few years indirect evidence of reactions between gaseous ions and molecules has come from radiation chemistry studies while similar information concerning ion-molecule interaction in condensed phases has long been available in the framework of the

[1] F. H. Field and J. L. Franklin, *Electron Impact Phenomena and the Properties of Gaseous Ions*. Academic Press, New York (1957).
[2] H. D. Smyth, *Rev. Mod. Phys.* **3**, 347 (1931).
[3] H. Eyring, J. O. Hirschfelder and H. S. Taylor, *J. Chem. Phys.* **4**, 479 (1936).

carbonium ion theory of organic chemical reactions. In this paper, however, we shall be concerned primarily with reactions that have been directly observed and shall mention sources of indirect evidence only in passing. As a further restriction in subject matter, we discuss only those reactions in which the ion kinetic energy is below about 5 eV. This excludes many studies of charge exchange, dissociative charge exchange, and collision-induced ion dissociations, which in a strict sense, are also ion-molecule reactions.

Experimental Techniques

In the usual ionization chamber of a mass spectrometer ions, formed by electron impact, are impelled out of the chamber by a small applied electric field. Under conventional analytical conditions the pressure in the ionization chamber is so low (10^{-5} to 10^{-6} mm) that a primary ion has no opportunity to collide with a molecule during its brief residence time (10^{-6} to 10^{-7} sec) in the chamber. Thus under these conditions one sees no secondary reactions, but rather only the primary mass spectrum, consisting of the parent ion and the various fragment ions characteristic of the breakdown pattern of the molecule. However, if the pressure in the ionization chamber is raised sufficiently the fraction of primary ions that suffers collisions with molecules during the average residence time becomes appreciable; often the result of these collisions is a chemical reaction which produces a new or secondary ion and an electrically neutral entity.

The criteria used to decide if an ion, that appears in a "high pressure" mass spectrum but not in the corresponding "low pressure" spectrum, is formed by a bimolecular gas phase reaction are twofold.[4,5] Firstly, the intensity of a secondary ion will increase with the square of the pressure whereas a primary ion intensity, including, of course, that of primary ions due to impurities, will increase with the first power of the pressure. Obviously, the ratio of the intensity of a secondary ion to that of a primary ion will increase as the first power of the pressure. Such behavior for the CH_5^+ and $C_2H_5^+$ secondary ions in methane is shown in Fig. 1.[4] The slight curvature exhibited by the data pertaining to the $C_2H_5^+$ ion is due to differential scattering in the analyser of the mass spectrometer; it is not a phenomenon that occurs in the ionization chamber (the reaction vessel in these studies) and is, therefore, of no consequence to this discussion. The second criterion is based upon an empirical fact;[4] it has been observed that the behavior of ions formed in a gas phase collision with variation in the electric field strength in the ionization chamber is different from ions formed by electron impact in the electron beam. This difference in behavior enables one to make a differentiation between secondary ions formed by a gas phase collision, and secondary ions formed by electron impact subsequent to some other process such as pyrolysis on the electron-emitting filament. This phenomenon is not understood but probably results from the secondary ions being formed in a different region of the ionization chamber than the primary ions.

Once having established a secondary ion to be due to a bimolecular gas phase collision, it is, of course, desirable to ascertain the chemical reaction that is involved. It is generally assumed that the electrically neutral species taking part in the reaction is one of the molecules introduced into the mass spectrometer. The identity of the

[4] F. H. Field, J. L. Franklin and F. W. Lampe, *J. Amer. Chem. Soc.* **79**, 2419 (1957).
[5] D. P. Stevenson and D. O. Schissler, *J. Chem. Phys.* **29**, 282 (1958).

ionic reactant is usually established by measurement of the ionizing electron energy at which the secondary ion first appears in the spectrum (appearance potential). The primary ion whose appearance potential most closely corresponds to that of the secondary ion is considered to be the ionic reactant,[4,5,7] provided that the reaction then visualized is not endothermic by more than one or two kcal/mole. This requirement of endothermicity is easily seen; in general, secondary ion abundances are quite small and, if we assume any reasonable collision cross-section, an exponential term involving

VOL. 7 1959

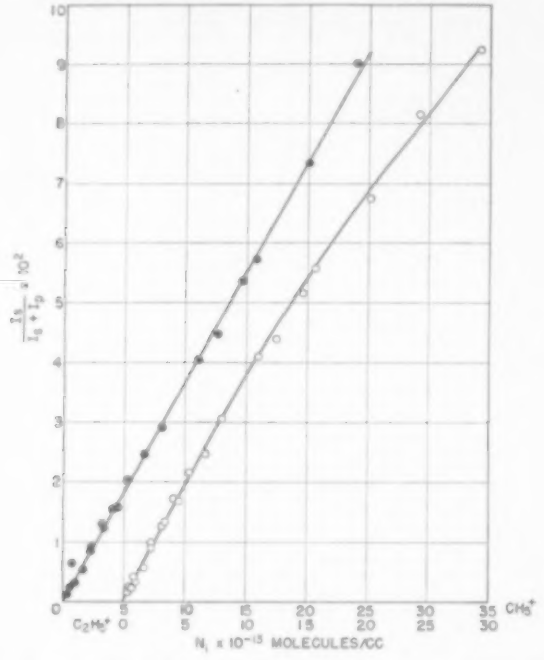

FIG. 1. Typical curves of current ratios against ion chamber concentration.

significant activation energy ($E_{act} \geqslant \Delta H_R$) would so decrease the probability of occurrence of a reactive collision that we could not detect a reaction. For further details of reaction identification the original papers should be consulted.[4–7]

A quantitative interpretation of the results, in terms of the usual kinetic quantities (specific reaction rate or reaction cross-sections), requires a knowledge of the gas concentration in the ionization chamber. This quantity is usually determined as a function of the more easily measured mass spectrometer reservoir pressure of the gas.[4,5,8] In this method the ionization cross-section of the gas under investigation is determined by comparison of the total positive ion-current produced in it to that produced in a gas of known total ionization cross-section under identical conditions and in the limit of zero pressure. With the total ionization cross-section of a gas known, measurement of the total ionization produced in it permits calculation of the ionization chamber concentration as a function of the manometrically measured

[6] V. L. Tal'roze and A. K. Lyubimova, *Dokl. Akad. Nauk SSSR* **86**, 909 (1952).
[7] V. L. Tal'roze and E. L. Frankevich, *Dokl. Akad. Nauk SSSR* **111**, 376 (1956).
[8] D. P. Stevenson and D. O. Schissler, *J. Chem. Phys.* **23**, 1353 (1955).

reservoir pressure. As a result of such measurements many ionization cross-sections for 75 eV are now recorded in the literature.[9,10]

Kinetics of Ion-Molecule Reactions

A. *Theory*

To convert the mass spectrometer ion-currents and measured ionization chamber concentrations for a given reaction into kinetic quantities, it is necessary to choose a model for the reaction. We consider[1] the reaction of a primary ion with a neutral molecule to consist of the formation of a transition-state ion which decomposes unimolecularly to various product ions and neutral entities. That is,

$$P^+ + M \xrightarrow{k_1} PM^+ \tag{1}$$

$$PM^+ \xrightarrow{k_{s_j}} S_j^+ + F_j \tag{2}$$

where there may be a set of the above reactions for each primary ion that undergoes reaction with molecules. If the time of decomposition of PM^+ is short compared with ionic residence times (that is, if $k_{s_j} \gg 10^6$–10^7 sec^{-1}) then we can write for the number of ions S_j formed

$$n_{s_j} = \frac{k_{s_j}}{\sum k_{s_j}} n_{PM} . \tag{3}$$

The number of ions, PM, formed is

$$n_{PM} = f\Omega[M]n^\circ{}_p \tag{4}$$

where $n^\circ{}_p$ = the number of primary ions formed
f = collision efficiency for formation of PM^+
Ω = total number of collisions made by a single primary ion with neutral molecules at unit concentration
$[M]$ = concentration of neutral molecules.

Combining (3) and (4) and introducing τ_p, the residence time of the primary ion in the ionization chamber, we get

$$\frac{n_{s_j}}{n^\circ{}_p} = \frac{k_{s_j}}{\sum_j k_{s_j}} \frac{f\Omega}{\tau_p} [M]\tau_p . \tag{5}$$

If the ratio of the number of secondary ions to the number of precursor primary ions is small (a condition always fulfilled), the quantity $(f\Omega)/(\tau_p)$ is the time-average rate of effective collisions, at unit concentrations, for PM^+ formation; this is, of course, the bimolecular rate constant k_1. Furthermore, $n^\circ{}_p = n_p + \sum_j n_{s_j}$, where n_p is the number of primary ions collected. Making the further assumption that the collection efficiencies of all ions are equal, (5) becomes

$$\frac{I_{s_j}}{I_p + \sum_j I_{s_j}} = \frac{k_{s_j}}{\sum_j k_{s_j}} k_1[M]\tau_p \tag{6}$$

[9] J. W. Otvos and D. P. Stevenson, *J. Amer. Chem. Soc.* **78**, 546 (1956).
[10] F. W. Lampe, J. L. Franklin and F. H. Field, *J. Amer. Chem. Soc.* **79**, 6129 (1957).

where the I's are the observed ion-currents. k_1 is easily evaluated from (6) by the additional relationship:

$$\frac{I_{s_1}}{\sum_j I_{s_j}} = \frac{k_{s_1}}{\Sigma k_{s_j}}. \tag{7}$$

Another often-used way of expressing the rate is by means of the reaction cross-section. It is easily shown that the quantity Ω, defined earlier, is equal to the product of the collision cross-section, Q_c, and the distance, x, that the primary ions travel from the time that they are formed in the electron beam to the time that they pass out of the ionization chamber. That is

$$f\Omega = fQ_c x. \tag{8}$$

Comparison of (5), (6), and (8) shows immediately that

$$k_1 = fQ_c \frac{x}{\tau_p}. \tag{9}$$

Assuming the primary ions to be formed, on the average, with zero velocity component in the degree of freedom corresponding to the direction of the electric field, the primary ion residence time is, from the laws of motion,

$$\tau_p = \left(\frac{2m_i d}{eE}\right)^{\frac{1}{2}} \tag{10}$$

where d is the distance between the center of the electron beam and the ion-exit slit, m_i is the mass of the ion, E is the electric field strength, and e is the electronic charge. Although x, the distance traveled by a primary ion in its path through the ionization chamber, is a function of E and becomes equal to d only in the limit of infinite field strength, at all practical field strengths employed it may be replaced by d with little error. Then combining (9) and (10) we get

$$k_1 = \left(\frac{eEd}{2m_i}\right)^{\frac{1}{2}} fQ_c \tag{11}$$

a result identical to that obtained from a much more elaborate derivation.[11]

Eyring *et al.*[3] have shown that for absolute reaction rate theory the interaction between a molecule and an ion is adequately represented by an inverse fourth power attractive potential. For this type of interaction the *collision* cross-section is inversely proportional to the square root of the initial kinetic energy of the collision partners.[4,11,12] Strictly speaking, the initial kinetic energy will be an additive function of the thermal energies of both ion and molecule and the kinetic energy due to the acceleration of the ion by the electric field. However, at the field strengths generally employed in ion-molecule reaction studies, the thermal energy contribution is negligibly small and the collision cross-section should vary inversely with the square root of the electric field strength. That is,

$$Q_c \propto \left(\frac{1}{E}\right)^{\frac{1}{2}}. \tag{12}$$

[11] G. Gioumousis and D. P. Stevenson, *J. Chem. Phys.* **29**, 294 (1958).
[12] M. A. Eliason, D. E. Stogryn and J. O. Hirschfelder, *Proc. Natl. Acad. Sci.* **42**, 546 (1956).

Comparison of (11) and (12) indicates that if the efficiency or probability factor of the reaction, f, is independent of reactant energy, the rate constant, k_1, is independent of electric field strength.

B. *Results*

Equations (6) and (9) indicate that if one plots the observed ion-current ratio versus the gas concentration a straight line having a slope equal to

$$\frac{k_{s_i}}{\sum_j k_{s_j}} fQ_c x$$

is obtained. Such plots for the reactions

$$CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3 \qquad \text{(R1)}$$

$$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2 \qquad \text{(R2)}$$

are shown in Fig. 1. As mentioned earlier the curvature in the plot for the $C_2H_5^+$ is a result of differential scattering[4] and is of no consequence in this discussion; in cases where differential scattering occurs the initial slope is used to determine rate quantities. For reactant ions which produce only one product ion, such as in (R1) and (R2), $k_{s_i}/\sum_j k_{s_j}$ is unity and fQ_c is obtained directly (taking $x = d$). Otherwise (7) must be used to evaluate $k_{s_i}/\sum_j k_{s_j}$. To express the results in terms of specific reaction rate (11) is used.

For a certain class of reactions (usually reactions involving H_2 or H_2^+) that obeys (12) specific reaction rates can be determined at constant concentration by study of the variation of ion-current ratio with electric field strength.[5,13] Generally, however, (12) is not obeyed[4,13,16] with the consequence that k_1 is a function of electric field strength, decreasing with increasing field. A semi-empirical attempt to rationalize the effect of electric field for those cases in which (12) is not obeyed has been made,[4] primarily to obtain an extrapolation function; however, no really satisfactory explanation has yet been advanced.

A further interesting kinetic question concerns the nature of the transition state ion. Is it better represented as a charged system of two molecular species, each of which retains its identity, held together by polarization forces, for example in the case of (R1) by

$$(CH_4 \ldots H^+ \ldots CH_4)$$

or is it better represented by a charged molecular system in which intimate mixing has occurred, that is, by $(C_2H_8)^+$?

Experiments with deuterated compounds suggest that both types of transition state ion exist. For the system CH_4—CD_4, Wagner *et al.*[17] have measured the relative abundances of CD_5^+, CD_4H^+, $CH_3D_2^+$, and CH_5^+ and have shown quite conclusively that no intimate mixing of hydrogen and deuterium occurs. Thus for this system the transition state ion is better represented by the first type of complex, that of individual molecular species physically bound together.

[13] D. P. Stevenson, *J. Phys. Chem.* **61**, 1453 (1957).
[16] F. W. Lampe, F. H. Field and J. L. Franklin, *J. Amer. Chem. Soc.* **79**, 6132 (1957).
[17] C. D. Wagner, P. A. Wadsworth and D. P. Stevenson, *J. Chem. Phys.* **28**, 517 (1958).

On the other hand, for systems in which the stoichiometry of the transition state corresponds to a stable ionic structure and in which much more atomic rearrangement occurs on reaction, the intimately mixed complex seems to be the appropriate model. The evidence for this is twofold: firstly, the agreement of the "secondary mass spectra" due to the reactions

$$C_2H_4^+ + C_2H_4 \rightarrow [C_4H_8]^+ \rightarrow \text{fragmentation} \quad \text{(R3)}$$

$$C_2H_2^+ + C_2H_4 \rightarrow [C_4H_6]^+ \rightarrow \text{fragmentation} \quad \text{(R4)}$$

$$C_2H_2^+ + C_2H_2 \rightarrow [C_4H_4]^+ \rightarrow \text{fragmentation} \quad \text{(R5)}$$

with the primary mass spectra of C_4H_8, C_4H_6, and C_4H_4 compounds is evidence of a chemically bound intermediate structure;[4,15] secondly, the relative abundances of the deuterated $C_3H_5^+$ ionic products in the reaction[18]

$$CD_4^+ + C_2H_4 \rightarrow [C_3H_4D_4]^+ \begin{cases} \xrightarrow{a} C_3H_4^+D + D_2 + D \\ \xrightarrow{b} C_3H_3D_2^+ + (2D + H) \\ \xrightarrow{c} C_3H_2D_3^+ + (2H + D) \\ \xrightarrow{d} C_3HD_4^+ + H_2 + H \end{cases} \quad \text{(R6)}$$

are a : b : c : d = 1 : 4 : 4 : 1. Completely equivalent hydrogen atoms in the complex would lead to 1 : 6 : 6 : 1. Thus in (R6) also it appears as if intimate mixing does occur and that the transition-state-ion is better represented by a chemically bound charged entity.

In the following sections of this paper we have tabulated the ion-molecule reactions observed to date. The reaction cross-sections reported are, in general, those obtained in our laboratory at a field strength of 10 V/cm. In the case of values reported by other workers[13,14] we have tabulated the cross-sections as reported for those reactions not obeying (12) and have converted the reported rate constants for those reactions obeying (12) to reaction cross-sections at 10 V/cm by means of equation (11). In comparing rate constants and cross-sections of ion-molecule reactions and in utilizing them in interpretations of similar reactions carried out in more conventional reaction vessels, it should be kept in mind that the reported values, in general, refer to an electric field strength and may be dependent upon field strength.

Ion-Molecule Reactions Observed

A. *Reactions involving neutral atom and positive atomic ion transfer*

This type of reaction includes those first observed by early workers in mass spectrometry and often results in a type of molecular species both new and interesting from a structural point of view, namely, the protonated molecular structures long postulated as intermediates in organic chemistry. In Table I we present the reactions known to date, along with the type of transfer involved, the reaction cross-section reported, and the observers. In cases in which more than one reaction cross-section

[14] D. O. Schissler and D. P. Stevenson, *J. Chem. Phys.* **24**, 926 (1956).
[15] F. H. Field, J. L. Franklin and F. W. Lampe, *J. Amer. Chem. Soc.* **79**, 2665 (1957).
[18] This Laboratory, Unpublished results.

TABLE I. NEUTRAL ATOM AND POSITIVE ATOMIC ION TRANSFER REACTIONS

Reaction	Entity transferred	$fQ_c \times 10^{16}$ cm^2	Reference
$H_2^+ + H_2 \rightarrow H_3^+ + H$	?	27·4[a]	3
$D_2^+ + D_2 \rightarrow D_3^+ + D$	?	26·8	8, 13
$H_2^+ + C_2H_4 \rightarrow H_3^+ + C_2H_3$	H.	—	19
$Ne^+ + H_2 \rightarrow NeH^+ + H$	H.	14·1	14
$A^+ + H_2 \rightarrow AH^+ + H$	H.	111	8, 13
$A^+ + HD \rightarrow AD^+ + H$	D.	46·3	8, 13
$A^+ + HD \rightarrow AH^+ + D$	H.	40·5	8, 13
$A^+ + D_2 \rightarrow AD^+ + D$	D.	82·1	8, 13
$Kr^+ + H_2 \rightarrow KrH^+ + H$	H.	42·5	13, 14
$Kr^+ + D_2 \rightarrow KrD^+ + D$	D.	29·8	14
$CH_4^+ + CH_4 \rightarrow CH_5^+ + CH_3$	?	61·0	4, 6, 20
$CD_4^+ + CD_4 \rightarrow CD_5^+ + CD_3$	?	63·4, 57·2	8, 17, 21
$(CD_4 + CH_4)^+ \rightarrow CH_4D^+ + CH_3$	?	73	21, 22
$(CH_4 + H_2)^+ \rightarrow CH_5^+ + H$	?	<0·2	19, 34
$CD_4^+ + C_2H_6 \rightarrow CD_4H^+ + C_2H_5$	H.	8·1	21, 22
$CH_4^+ + C_2H_6 \rightarrow CH_5^+ + C_2H_5$	H.	—	19
$CD_4^+ + C_2H_6 \rightarrow CD_4H^+ + C_2H_7$	H.	4	21, 22
$CD_4^+ + i\text{-}C_4H_{10} \rightarrow CD_4H^+ + C_4H_9$	H.	3	21, 22
$CD_4^+ + CH_3Cl \rightarrow CD_3H^+ + CH_2Cl$	H.	3	21, 22
$CD_4^+ + NH_3 \rightarrow CD_3H^+ + NH_2$	H.	6·4	21, 22
$CD_4^+ + H_2S \rightarrow CD_4H^+ + HS$	H.	12	21, 22
$(CH_4 + HCl)^+ \rightarrow CH_5^+ + Cl$	?	33[b]	21
$(CD_4 + HCl)^+ \rightarrow CD_4H^+ + Cl$	?	41[b]	21, 22
$C_2H_2^+ + C_2H_4 \rightarrow C_2H_3^+ + C_2H_3$	H^+	32, 359[c]	4, 13, 14
$C_3H_4^+ + C_2H_4 \rightarrow C_2H_5^+ + C_3H_3$	H^+	—	23
$C_3H_6^+ + C_2H_6 \rightarrow C_2H_7^+ + C_3H_5$	?	—	6, 14
$i\text{-}C_4H_8^+ + i\text{-}C_4H_8 \rightarrow t\text{-}C_8H_9^+ + C_4H_7$	?	—	6
$N_2^{+*} + N_2 \rightarrow N_2^+ + N$	?	—	24, 25
$N_2^+ + D_2 \rightarrow N_2D^+ + D$	D.	86·3	13, 14
$NH_3^+ + NH_3 \rightarrow NH_4^+ + NH_2$	?	—	18, 26
$O_2^+ + H_2 \rightarrow H_2O^+ + O$	O^+	—	27
$H_2O^+ + H_2O \rightarrow H_3O^+ + OH$	?	95·0	6, 7, 16
$D_2O^+ + D_2O \rightarrow D_3O^+ + OD$	?	102	16
$D_2O^+ + H_2 \rightarrow HD_2O^+ + H$	H	63·0	16
$(H_2O + CH_4)^+ \rightarrow H_3O^+ + CH_3$	?	180	6, 16
$(D_2O + CH_4)^+ \rightarrow HD_2O^+ + CH_3$	?	148	16
$H_2O^+ + C_2H_2 \rightarrow H_3O^+ + C_2H$	?	—	7
$C_2H_6^+ + D_2O \rightarrow HD_2O^+ + C_2H_5$	H^+	440	16
$D_2O^+ + \text{cyclo } C_3H_6 \rightarrow HD_2O^+ + C_3H_5$	H.	40	16
$H_2O^+ + C_3H_8 \rightarrow H_3O^+ + C_3H_7$	H.	—	7
$C_3H_8^+ + H_2O \rightarrow H_3O^+ + C_3H_7$	H^+	—	7

TABLE 1 (*continued*)

Reaction	Entity transferred	$fQ_c \times 10^{16}$ cm^2	Reference
$C_3H_8^+ + D_2O \rightarrow HD_2O^+ + C_3H_7$	H^+	440	16
$D_3O^+ + n\text{-}C_4H_{10} \rightarrow HD_2O^+ + C_4H_9$	H.	96	16
$H_2O^+ + NH_3 \rightarrow H_3O^+ + NH_2$	H.	—	7
$H_2O^+ + H_2S \rightarrow H_3O^+ + HS$	H.	—	7
$H_2S^+ + H_2O \rightarrow H_3O^+ + HS$	H^+	—	7
$H_2^+ + O_2 \rightarrow HO_2^+ + H$	H^+	126	13, 14
$D_2^+ + O_2 \rightarrow DO_2^+ + D$	D^+	88	13, 14
$CO^+ + D_2 \rightarrow CDO^+ + D$	D.	72·5	14
$CH_3OH^+ + CH_3OH \rightarrow CH_3OH_2^+ + CH_3O$	?	583	13, 14
$CH_3OH^+ + H_2O \rightarrow CH_3OH_2^+ + OH$	H.	—	23
$C_2H_5OH^+ + H_2O \rightarrow C_2H_5OH_2^+ + OH$	H.	—	23
$(CO_2 + H_2)^+ \rightarrow HCO_2^+ + H$	?	—	29
$H_2O^+ + CO_2 \rightarrow HCO_2^+ + OH$	H^+	—	29
$O^+ + N_2 \rightarrow NO^+ + N$	N.	2000[e]	30
$HCl^+ + HCl \rightarrow H_2Cl^+ + Cl$	?	24, 48	14, 21
$(HCl + CH_4)^+ \rightarrow H_2Cl^+ + CH_3$	?	129[f]	21
$(HCl + CD_4)^+ \rightarrow HDCl^+ + CD_3$	?	109[f]	21
$CH_3Cl^+ + CH_3Cl \rightarrow CH_4Cl^+ + CH_2Cl$	?	—	18
$HBr^+ + HBr \rightarrow H_2Br^+ + Br$	?	39	14
$H_2S^+ + H_2S \rightarrow H_3S^+ + HS$	?	31	21, 22
$H_2S^+ + CD_4 \rightarrow H_2DS^+ + CD_3$	D.	14	21, 22

[a] Theoretical calculation of k_1 combined with equation (11).
[b] Calculated on the assumption that CH_4^+ (or CD_4^+) is the ionic reactant.
[c] Probably at about 8 V/cm.
[d] Calculated on the assumption that H_2O^+ (or D_2O^+) is the ionic reactant.
[e] Very uncertain.
[f] Calculated on the assumption that HCl^+ is the ionic reactant.

[19] E. L. Frankevich and V. L. Tal'roze, *Dokl. Akad. Nauk SSSR* **119**, 1174 (1958).
[20] G. G. Meisels, W. H. Hamill and R. R. Williams, Jr., *J. Chem. Phys.* **25**, 790 (1956).
[21] F. H. Field and F. W. Lampe, *J. Amer. Chem. Soc.* **80**, 5583 (1958).
[22] F. W. Lampe and F. H. Field, *J. Amer. Chem. Soc.* **79**, 4244 (1957).
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[24] M. Saporoschenko, *Phys. Rev.* **111**, 1550 (1958).
[25] G. Junk and H. J. Svec, *J. Amer. Chem. Soc.* **80**, 2908 (1958).
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[27] D. A. Hutchinson, Paper presented at *Amer. Chem. Soc. Meeting*, Minneapolis, Minnesota, Sept. (1955).
[28] M. M. Mann, A. Hustrulid and J. T. Tate, *Phys. Rev.* **58**, 340 (1940).
[29] J. J. Mitchell, R. H. Perkins and F. F. Coleman, *J. Chem. Phys.* **16**, 835 (1948).
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[31] F. W. Lampe and F. H. Field, *J. Amer. Chem. Soc.* **81**, 3238 (1959).

VOL. 7 1959

have been reported, we tabulate all available values. For cases in which reactants are written as $(A + B)^+$ we do not know which of the species is the ionic reactant.

Although the theory of the rates of ion-molecule reactions gives order-of-magnitude agreement with observation, the deviations in rate from one reaction to another are not, in general, accounted for by the theory.

It is perhaps of interest to point out that the cross-sections of those reactions in Table 1 that are known to involve the transfer of a proton are usually an order of

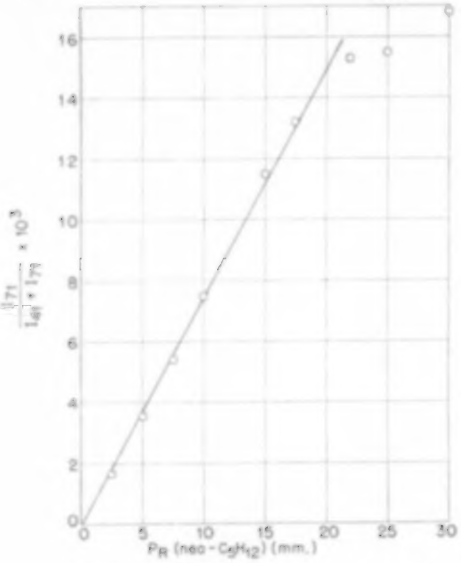

FIG. 2. Hydride ion transfer in neopentane.

magnitude larger than those involving the transfer of a hydrogen atom. Again, this fact is not explainable by the present theory of ion-molecule reaction rates.

B. *Hydride ion transfer reactions*

Reactions involving the transfer of a hydride ion have been postulated for many years[31,32] and are considered to be of much importance in many processes such as alkylation, isomerization and cationic polymerization. Prior to their detection in the gas phase,[33] however, there had never been, to our knowledge, direct observation of the elementary reactions.

Recognition of the fact that hydride ion transfer reactions were occurring in the gas phase was due to the observation that in many paraffinic compounds the "high pressure" mass spectra show secondary ions of mass one unit lower than the molecular weight of the parent compound. The phenomenon is most obvious (and was here first observed) in neopentane because in this system the primary ions containing five carbon atoms have a negligible intensity; hence any secondary ions formed in this mass region will not be obscured. In Fig. 2[33] we show a plot of the ratio of the mass

[31] P. D. Bartlett, F. E. Condon and A. Schneider, *J. Amer. Chem. Soc.* **66**, 1531 (1944).
[32] F. C. Whitmore, *J. Amer. Chem. Soc.* **54**, 3274 (1932).
[33] F. H. Field and F. W. Lampe, *J. Amer. Chem. Soc.* **80**, 5587 (1958).

71 intensity to the sum of the intensities of the mass 71 and mass 41 ions against the neopentane pressure. The rise of this ratio shows without doubt that $C_5H_{11}^+$ is a secondary ion. The appearance potential of the $C_5H_{11}^+$ ion is identical to the appearance potential of the $C_3H_5^+$ primary ion from neopentane[34] and it may be concluded that $C_3H_5^+$ is a reactant ion. Any reaction between $C_3H_5^+$ ion and neopentane to form the $C_5H_{11}^+$ ion that does not involve the formation of propylene would be strongly endothermic and hence not observable by mass spectrometric technique. Therefore, the reaction occurring must be

$$C_3H_5^+ + \text{neo}C_5H_{12} \rightarrow C_5H_{11}^+ + C_3H_6 \qquad \text{(R7)}$$

which is obviously a hydride ion transfer reaction.

Although appearance potential measurements establish $C_3H_5^+$ as a reactant ion they do not rule out the possibility that other ions of higher appearance potentials may also be reactant ions. In view of its simple nature it seems likely that the reaction will occur with all ions having an unoccupied valence orbital, provided that it is not energetically prohibited. In this respect it is of interest to point out that appearance potential measurements do rule out the occurrence of the reaction

$$\text{t-}C_4H_9^+ + \text{neo}C_5H_{12} \rightarrow \text{iso}C_4H_{10} + C_5H_{11}^+. \qquad \text{(R8)}$$

Since the lack of occurrence of (R8) cannot be due to intensity limitations (t-$C_4H_9^+$ is the major primary ion) it may be limited energetically; an endothermicity of 2 kcal/mole would certainly preclude its observation. Taking the most reliable value of ΔH_f(t-$C_4H_9^+$) to be 178 kcal/mole[34,46] would then lead to $\Delta H_f(C_5H_{11}^+) \geqslant 168$ kcal/mole.

Secondary ions of mass one unit less than the parent molecule also have been observed in ethane, propane, n-butane, isobutane, and neohexane. However, for these compounds no experimental information concerning the details of the reactions is available because of the presence of appreciable quantities of primary ions having masses one unit less than the parent molecule. The identities of the neutral reactant and product ion are known, though, and coupled with energetic considerations permit the assignment of some limits upon the possible ionic reactants and neutral products. In Table 2[33] we show the possible hydride ion transfer reactions that account for the observations. The list of possible ionic reactants was arrived at by assuming that only exothermic reactions of primary ions having abundances of 10 per cent or greater need be considered. It should be recognized that in some instances sufficient energy will be available for further decomposition of the neutral product.

Studies of hydride ion transfer reactions have also been made with the same pure compounds admixed with methane.[33] Since the only ions from methane which can undergo the reaction are the CH_2^+ and CH_3^+ ions, there is less uncertainty concerning the reactions involved in removing a hydride ion from the parent molecule. These systems are also listed in Table 2 and a typical plot for the i-C_4H_{10}—CH_4 mixtures is shown in Fig. 3.

Values of reaction cross-section listed in Table 2 were obtained by assuming the reactant ions to be those primary ions of more than 10 per cent relative intensity

[46] F. P. Lossing, P. Kebarle and J. B. Desousa, Paper presented at the Institute of Petroleum Hydrocarbon Research Group and A.S.T.M. Committee E-14 Joint Conference on *Mass Spectrometry*, London, September (1958).

TABLE 2. HYDRIDE ION TRANSFER REACTIONS

System	Allowed reactant ions	Reaction cross-section (A^2)
C_2H_6	CH_3^+, $C_2H_5^+$	264
C_3H_8	CH_3^+, $C_2H_5^+$, $C_2H_4^+$, $C_2H_5^+$, $C_3H_3^+$, $C_3H_5^+$	66
n-C_4H_{10}	$C_2H_5^+$, $C_2H_4^+$, $C_2H_5^+$, $C_3H_3^+$, $C_3H_5^+$, $C_3H_6^+$, $C_3H_7^+$	32
i-C_4H_{10}	$C_2H_5^+$, $C_3H_3^+$, $C_3H_5^+$, $C_3H_6^+$, $C_3H_7^+$	34
neo-C_5H_{12}	$C_2H_5^+$, $C_3H_5^+$, $C_3H_6^+$, $C_5H_5^+$	14
neo-C_6H_{14}	$C_2H_5^+$, $C_3H_5^+$, $C_3H_6^+$, $C_3H_7^+$, $C_4H_5^+$, $C_4H_9^+$, $C_5H_{11}^+$	7
C_2H_6–CH_4	CH_3^+, CH_2^+	171
C_3H_8–CH_4	CH_3^+, CH_2^+	107
n-C_4H_{10}–CH_4	CH_3^+, CH_2^+	60
i-C_4H_{10}–CH_4	CH_3^+, CH_2^+	101
neo-C_5H_{12}–CH_4	CH_3^+, CH_2^+	12
neo-C_6H_{14}–CH_4	CH_3^+, CH_2^+	16

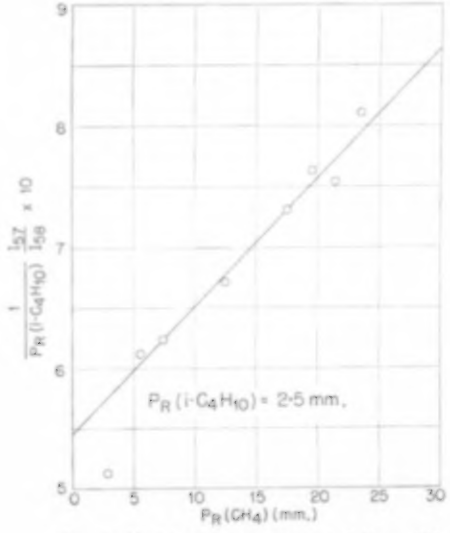

FIG. 3. Hydride ion transfer in i-C_4H_{10}—CH_4.

which are energetically capable of reaction, for the case of the pure compounds, and CH_2^+ and CH_3^+ for the methane mixtures. Slopes of ion-current ratios versus pressure plots (Figs. 2 and 3) were then compared to slopes observed for (R1), for the calculation of reaction cross-sections. The cross-sections so calculated depend strongly upon the correctness of the assumption of which ions are reactants. Consequently, the agreement between the values found for the pure compounds and methane mixtures, while certainly not exact, may be considered as satisfactory. In both sets of values there is a trend of decreasing reaction cross-section with increasing molecular weight. We have no explanation for this trend which is in the direction opposite to that expected.

In a sense the reactions observed by Meisels *et al.*,[20,35] viz.

$$A^+ + CH_4 \rightarrow CH_3^+ + H + A \quad \text{(R9)}$$

$$Kr^+ + CH_4 \rightarrow CH_3^+ + H + Kr \quad \text{(R10)}$$

$$Kr^+ + C_2H_6 \rightarrow C_2H_5^+ + H + Kr \quad \text{(R11)}$$

$$Xe^+ + C_3H_8 \rightarrow C_3H_7^+ + H + Xe \quad \text{(R12)}$$

could be considered as hydride ion transfers resulting in an unstable molecule which immediately dissociates. However, there may be some question about (R10) since if it occurs without any excess energy in Kr^+ it is the first endothermic reaction observed ($\Delta H = +7$ kcal/mole). Moreover, since the parent peaks in the methane, ethane, and propane spectra for the systems indicated in (R10)–(R12) also increase with rare gas pressure,[35] these reactions are best considered as dissociative charge transfer processes.

VOL. 7 1959

C. *Condensation type reactions*

Under this heading we group all those reactions that involve considerably more molecular rearrangement than the simple transfer of an atom or atomic ion. In all reactions of this class, observed to date, carbon–carbon or carbon–sulfur bond formation occurs; hence the use of the term condensation. The reactions reported along with their specific reaction rates are shown in Table 3.

In addition to the reactions listed in Table 3, Levy and Skahan[40] have found secondary ions in *cis*-2-butene, the most prominent of which were the $C_5H_7^+$ and $C_5H_9^+$ ions. As has proven to be generally true, they found no dimer ions ($C_8H_{16}^+$) but did observe ion masses up to 105.

Many of the reactions shown in Table 3 are of an unexpected and even surprising nature. Knowledge of the existence of such reactions is proving of considerable aid in radiation chemistry mechanism studies because such unusual reactions would never be postulated on an a priori basis. Of course, their importance in other reaction systems depends upon whether or not the reactant ions are formed.

D. *Negative ion reactions*

As is true in studies of the properties of isolated ions in the gas phase and organic chemical reactions in condensed phases, much more is known about bimolecular positive ion reactions than the corresponding negative ion reactions. To the authors' knowledge there have been only two negative ion-molecule reactions observed to date (other than collision induced dissociations at high ion energies), namely,

$$H^- + H_2O \rightarrow OH^- + H_2. \quad \text{(R13)}[41]$$

and

$$HCOO^- + N_2 \rightarrow CN^- + (HNO_2?) \quad \text{(R14)}[42]$$

Reaction (R13) is probably most easily visualized as the transfer of a proton from the water to the hydride ion.

[35] G. G. Meisels, W. H. Hamill and R. R. Williams, Jr., *J. Phys. Chem.* **61**, 1456 (1957).
[40] E. J. Levy and D. J. Skahan, Paper presented at Meeting of A.S.T.M. Committee E-14 on *Mass Spectrometry*, New Orleans, Louisiana, June (1958).
[41] E. E. Muschlitz, *J. Appl. Phys.* **28**, 1414 (1957).
[42] C. E. Melton and Gus A. Ropp, *J. Amer. Chem. Soc.* **80**, 5573 (1958).

TABLE 3. CONDENSATION TYPE REACTIONS

Reaction	$fQ_c \times 10^{16}$ cm^3	Reference
$CH_3^+ + CH_4 \rightarrow C_2H_5^+ + H_2$	58, 165[a]	4, 13, 14, 20, 35
$CD_3^+ + CD_4 \rightarrow C_2D_5^+ + D_2$	161[a]	13, 14, 18
$CH^+ + C_2H_2 \rightarrow C_3H^+ + H_2$	39	15
$CH^+ + C_2H_2 \rightarrow C_3H_2^+ + H$	19	15
$C_2H_2^+ + C_2H_4 \rightarrow C_3H_3^+ + CH_3$	22, 24[a]	4,14
$C_2H_4^+ + C_2H_4 \rightarrow C_3H_5^+ + CH_3$	43, 112[a]	4, 13, 14
$C_2H_3^+ + C_2H_6 \rightarrow C_3H_5^+ + CH_4$	78[a]	14
$CH_4^+ + C_2H_4 \rightarrow C_3H_6^+ + H_2 + H$	—	18
$CD_4^+ + C_2H_4 \rightarrow C_3H_4D^+ + D_2 + D$	—	18
$CD_4^+ + C_2H_4 \rightarrow C_3H_3D_2^+ + (2D + H)$	—	18
$CD_4^+ + C_2H_4 \rightarrow C_3H_2D_3^+ + (2H + D)$	—	18
$CD_4^+ + C_2H_4 \rightarrow C_3HD_4^+ + H_2 + H$	—	18
$C_2^+ + C_2H_2 \rightarrow C_4H^+ + H$	68	15
$C_2H_2^+ + C_2H_2 \rightarrow C_4H_2^+ + H_2$	35	15
$C_2^+ + C_2H_4 \rightarrow C_4H_2^+ + H_2$	89	4
$C_2H_2^+ + C_2H_2 \rightarrow C_4H_3^+ + H$	42	15
$C_2H^+ + C_2H_4 \rightarrow C_4H_3^+ + H_2$	34	4
$C_2H_2^+ + C_2H_4 \rightarrow C_4H_5^+ + H$	14	4
$C_2H_4^+ + C_2H_4 \rightarrow C_4H_7^+ + H$	4	4
$C_3H_5^+ + C_3H_6 \rightarrow C_4H_7^+ + C_2H_4$	140[a]	13, 14
$C_3H_6^+ + C_3H_6 \rightarrow C_4H_8^+ + C_2H_4$	74[a]	13, 14
$C_3H_3^+ + C_4H_6 \rightarrow C_7H_7^+ + C_2H_2$	—	39
$C_4H_6^+ + C_4H_6 \rightarrow C_7H_9^+ + C_3H_3$	—	39
$C_4H_6^+ + C_4H_6 \rightarrow C_7H_9^+ + C_3H_5$	—	39
$C_4H_3^+ + C_4H_6 \rightarrow C_7H_7^+ + C_2H_4$	—	39
$C_4H_4^+ + C_4H_6 \rightarrow C_7H_8^+ + C_2H_3$	—	39
$C_4H_5^+ + C_4H_6 \rightarrow C_7H_9^+ + C_2H_2$	—	39
$C_4H_6^+ + C_4H_6 \rightarrow C_7H_7^+ + C_2H_5$	—	39
$C_4H_6^+ + C_4H_6 \rightarrow C_7H_8^+ + C_2H_4$	—	39
$C_2H_3^+$ or $C_4H_5^+$ $+ C_5H_6 \rightarrow C_7H_7^+ +$ C_2H_2 or CH_4 or H	—	39
$C_4H_5^+ + C_4H_6 \rightarrow C_7H_9^+ +$ CH_3	—	39
$CH_3^+ + H_2S \rightarrow CHS^+ + 2H_2$	(16)	21
$CH_4^+ + H_2S \rightarrow CHS^+ + 2H_2 + H$		21
$CH_3^+ + H_2S \rightarrow CH_3S^+ + H_2$	(52)	21
$CH_4^+ + H_2S \rightarrow CH_3S^+ + H_2 + H$		21

[a] Probably at about 8 V/cm.

[36] F. W. Lampe, *J. Amer. Chem. Soc.* **79**, 1055 (1957).
[37] F. W. Lampe, *Rad. Res.* **10**, 691 (1959).
[38] R. H. Schuler, *J. Chem. Phys.* **26**, 425 (1957).
[39] R. Barker, R. R. Williams, Jr. and W. H. Hamill, Paper presented at Meeting of A.S.T.M. Committee E-14 on *Mass Spectrometry*, New Orleans, Louisiana, June (1958).

The reaction cross-section for (R13) was found to be $3 \overset{\circ}{\times} 10^{-17}$ cm^2 which corresponds to a rate constant comparable to those observed in positive ion-molecule reaction studies.

Ion Energetics

As mentioned earlier the observance of a secondary ion enables one to conclude, within an error of one or two kcal/mole, that for the reaction involved in its formation, $\Delta H \leq O$. If the reaction producing the secondary ion can be established and if the standard heats of formation of reactants and neutral product(s) are known, upper limits to the heats of formation of the product ions may be calculated by the use of Hess's Law of constant heat summation. That is,

$$\Delta H_f(\text{product ion}) \leq \Sigma \Delta H_f(\text{reactants}) - \Sigma \Delta H_f(\text{neutral products}). \quad (13)$$

Contrary to one point of view,[23] however, this requirement that $\Delta H \leq O$ is a necessary but is not a sufficient condition for the observation of a given reaction. Thus the failure to detect a given reaction does not permit one to conclude without qualification that the reaction is endothermic. There may be other factors involved which result in failure to observe a given reaction. One possibility is the occurrence of a more probable competitive reaction; an example of this is provided by the finding of Meisels *et al.*[20,35] that A^+ undergoes a dissociative charge transfer reaction with methane rather than the hydrogen atom abstraction reaction which would be energetically equivalent to the established formation of AH^+ in argon–hydrogen mixtures.[8] Another possibility and one which may account for the failure to observe $C_2H_7^+$ and $C_3H_9^+$ ions in ethane–hydrogen and propane–hydrogen mixtures,[23] respectively, is that of the very rapid further decomposition of a highly energetic product ion formed in a very exothermic reaction. An extreme example of this alternative is the complete failure so far to detect the dimer ion formed by the association of the reactants. Lower limits to the heats of formation of product ions, derived from the assumption that a given reaction is endothermic because it is not observed, are therefore to be regarded with reservation. In Table 4 we present limits to the heats of formation of ions, for which, for the most part, no energetic values from independent methods are available. For the most part the upper limits are derived from the reactions known to take place which we have tabulated in Tables 1 and 3. The ΔH_f limits for the protonated paraffins other than methane are based on the reasonable assumption that in the hydride ion transfer reactions observed in methane mixtures, CH_3^+ is a reactant ion. The transition state ion in this case must be of the formula $C_nH_{2n+3}^+$ and in order for reaction to be observable its heat of formation must be lower than the sum of the heats of formation of the reactants. The values for $CH_3SH_2^+$, $CH_4SH_2^+$, $C_6H_{11}^+$, $C_6H_{12}^+$, and $C_8H_{17}^+$ were derived in a similar way.

Many of the ions shown in Table 4 have the structure of stable and often saturated molecules to which a proton has been added and it is of interest to express the energetics of such important and unusual species as proton affinities of the original molecule.[6–8,19,23] Since the proton affinity of a molecule, M, is defined as the negative of the enthalpy change of the reaction

$$M + H^+ \rightarrow MH^+ \quad (R15)$$

it follows that

$$P.A.(M) = \Delta H_f(H^+) + \Delta H_f(M) - \Delta H_f(MH^+). \quad (14)$$

TABLE 4. STANDARD HEATS OF FORMATION OF GASEOUS IONS

Ion	ΔH_f in kcal/mole	
	Ion-molecule reactions	Independent method
NeH^+	< 445	None
AH^+	< 312	None
KrH^+	< 271	None
H_3^+	$286^a < \Delta H_f < 304$	311[42]
CH_5^+	$218^a < \Delta H_f < 233$	None
$C_2H_7^+$	< 244	None
$C_3H_9^+$	< 242	None
$C_4H_{11}^+$	< 237	None
$C_5H_9^+$	< 309	226[1]
$C_5H_6^+$	< 261	231[1]
$C_5H_7^+$	< 233	226[1]
$C_5H_{13}^+$	< 232	None
$C_6H_4^+$	< 366	329[1]
$C_6H_7^+$	$201^a < \Delta H_f < 241$	None
$C_6H_8^+$	< 254	None
$C_6H_{11}^+$	< 230	None
$C_6H_{12}^+$	< 236	197–211[1]
$C_6H_{13}^+$	< 222	None
$C_7H_7^+$	< 330	215–244[1]
$C_7H_8^+$	< 281	215[1]
$C_7H_9^+$	< 235	None
$C_7H_{17}^+$	< 218	None
$C_8H_{17}^+$	< 190	None
N_2^+	< 398	388[44]
N_2H^+	< 307	278[44]
NH_4^+	< 180	154[45]
HO_2^+	< 304	271[1]
H_3O^+	$136^a < \Delta H_f < 140$	None
CHO^+	< 245	203[1]
$CH_3OH_2^+$	$134^a < \Delta H_f < 140$	None
$C_2H_5OH_2^+$	$107^a < \Delta H_f < 124$	None
HCO_2^+	< 156	140–195[1]
H_2Cl^+	< 225	None
H_2Br^+	< 226	None
H_2S^+	< 187	None
$CH_3SH_2^+$	< 257	None
$CH_4SH_2^+$	< 280	None

[a] Lower limit obtained by assumption that a reaction was endothermic because it was not observed. This is to be accepted with reservation.

[42] R. S. Baker, J. C. Giddings and H. Eyring, *J. Chem. Phys.* **23**, 344 (1955).
[44] J. L. Franklin, V. H. Dibeler, R. M. Reese and M. Kraus, *J. Amer. Chem. Soc.* **80**, 298 (1958).
[45] F. D. Rosini, D. D. Wagman, W. H. Evans, Samuel Levine, and I. Jaffe, *Selected Values of Chemical Thermodynamic Properties*. N.B.S. Circular 500 (1952).

VOL. 7 1959

TABLE 5. PROTON AFFINITIES OF MOLECULES IN GAS PHASE

Molecule	Proton affinity (kcal/mole)		Independent method
	Lower limit	Upper limit	
Ne	−80	—	—
A	43	—	—
Kr	94	—	—
H_2	61	79[a]	—
CH_4	114	129[a]	—
C_2H_6	101	—	—
C_3H_8	98	—	—
C_4H_{10}	98	—	—
cyclo-C_3H_6	164	—	—
C_5H_{12}	98	—	—
C_6H_6	144	—	—
cyclo-C_6H_{10}	132	—	—
C_6H_{14}	103	—	—
C_7H_8	142	—	—
C_7H_{16}	102	—	—
C_8H_{16}	155	—	—
N_2	58	—	—
NH_3	174	—	200[4,5]
O_2	61	—	—
H_2O	167	171[a]	—
CO	94	—	136[3]
CH_3OH	177	183[a]	—
C_2H_5OH	185	202[a]	—
CO_2	115	—	76–131[3]
HCl	120	—	—
HBr	130	—	—
H_2S	175	—	—
CH_3SH	105	—	—

[a] Upper limit obtained by assumption that a reaction was endothermic because it was not observed. This is to be accepted with reservation.

The data in Table 4 which represent upper and lower limits to $\Delta H_f(MH^+)$ can be used in (14) to calculate lower and upper limits, respectively, of the affinity of the original molecule, M, for the proton. In Table 5 we show proton affinity limits for those stable molecules whose protonated forms, MH^+, appear in Table 4. The reservation concerning the lower limits to the standard heats of formation of the ions applies to the upper limits of molecular proton affinities.

As expected the proton affinities of unsaturated molecules and of molecules containing unshared electron pairs are quite high (usually greater than 140 kcal/mole) and considerably higher than those of the saturated molecules. Nevertheless the proton affinities of the saturated molecules are surprisingly high. The protonation of saturated molecules is now being recognized as important in the radiation chemistry of gases and it may well be that such protonation plays a larger part than generally considered in chemical reactions in condensed phases that proceed by ionic mechanisms.

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REARRANGEMENT STUDIES WITH ^{14}C—VIII*

EXTERNAL AND INTERNAL RETURNS IN THE SOLVOLYSIS OF 2-PHENYL-1-^{14}C-ETHYL *p*-TOLUENESULFONATE

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Abstract—Acetolysis and formolysis of 2-phenyl-1-^{14}C-ethyl *p*-toluenesulfonate (I) were interrupted when the reactions were about 50 per cent complete. All samples of 2-phenylethyl *p*-toluenesulfonate recovered from the partially solvolyzed mixtures showed some rearrangements of the ^{14}C-labeled atoms from the C-1 to the C-2 positions, indicating the occurrence of some return to covalent bonding through the intermediate ethylphenonium ion (V) or its equivalent. The fraction of V undergoing return as compared to the amount of V involved in product formation was greater for acetolysis than formolysis. The presence of lithium perchlorate gave rise to salt-promoted ionization resulting in an increase in the ^{14}C rearrangement for the reaction products; however, lithium perchlorate also reduced the relative extent of return involving V. Solvolysis of I in the presence of sodium *p*-toluene-^{35}S-sulfonate made possible the simultaneous determinations of ^{14}C rearrangement and ^{35}S exchange in the recovered 2-phenylethyl *p*-toluenesulfonate. Considerations of such data led to the conclusion that both external and internal returns take place during acetolysis and formolysis of I.

IN a previous paper[1] on isotope position rearrangements observed in the products of solvolyses of 2-phenyl-1-^{14}C-ethyl *p*-toluenesulfonate (I), conclusions were drawn on the degrees of phenyl participation during solvolysis in different solvents. These results have been substantiated by Saunders *et al.*[2] from their studies on the rates of solvolysis of some deuterated 2-phenylethyl *p*-toluenesulfonates. It has also been noted[1] that a small amount of "unreacted" 2-phenylethyl *p*-toluenesulfonate recovered from the ethanolysis mixture showed rearrangement to almost the same extent as the ethanolysis product. Such rearrangements in the recovered sulfonate was tentatively attributed to the phenomenon of internal return involving an ethylphenonium *p*-toluenesulfonate ion-pair. In the present studies, acetolysis and formolysis of I were interrupted when the reactions were about 50 per cent complete, and the rearrangements of the ^{14}C-labeled atoms from the C-1 to the C-2 positions were determined for the reaction products and for the *p*-toluenesulfonate recovered from the reaction mixtures. The changes in the magnitude of these rearrangements brought about by effecting the solvolyses in the presence of added lithium perchlorate were also investigated. As an attempt to shed further light on a possible differentiation between external and internal returns, the acetolysis and formolysis of I were carried out in the presence of ^{35}S-labeled sodium *p*-toluenesulfonate, thus affording the simultaneous determinations of the rearrangement of ^{14}C-labeled atoms as well as the exchange of ^{35}S-labeled p-toluenesulfonate anion in the 2-phenylethyl *p*-toluenesulfonate recovered from the interrupted reactions.

* For paper VII, see A. J. Finlayson and C. C. Lee, *Canad. J. Chem.* **37**, 940 (1959).
† Holder of Canadian Industries Limited Fellowship, 1956–1958.
[1] C. C. Lee, G. P. Slater and J. W. T. Spinks, *Canad. J. Chem.* **35**, 1417 (1957).
[2] W. H. Saunders, Jr., S. Asperger and D. H. Edison, *J. Amer. Chem. Soc.* **80**, 2421 (1958).

VOL. 7 1959

RESULTS

2-Phenyl-1-^{14}C-ethyl *p*-toluenesulfonate (I) was prepared as previously described.[1] The location of the ^{14}C labels on the C-1 position was established by reaction of I with sodium iodide in acetone to give 2-phenyl-1-^{14}C-ethyl iodide which was oxidized to produce nonradioactive benzoic acid. Alternatively, the 2-phenyl-1-^{14}C-ethyl iodide so obtained was converted to the Grignard reagent followed by reaction with carbon dioxide to give hydrocinnamic acid which also oxidized to nonradioactive benzoic acid. The latter method was used for the degradation of the samples of 2-phenylethyl *p*-toluenesulfonate recovered from the interrupted solvolysis reactions because firstly, it affords a further purification of the 2-phenylethyl iodide through

TABLE 1. RESULTS FROM PARTIAL SOLVOLYSIS OF 2-PHENYL-1-^{14}C-ETHYL *p*-TOLUENESULFONATE

Reaction	Added salt[c]	% Rearrangement in product		% Rearrangement in recovered sulfonate		Rearrangement ratio (rearrangement in recovered sulfonate/ rearrangement in product)		% ^{35}S in Recovered sulfonate	
		Run 1	Run 2	Run 1	Run 2	Run 1	Run 2	Run 1	Run 2
Acetolysis[a]	None	4·8	4·4	2·0	1·9	0·41	0·43		
	0·05 M $LiClO_4$	5·4	5·3	2·1	2·1	0·39	0·40		
	0·5 M $LiClO_4$	11·9	11·1	2·6	2·1	0·22	0·19		
	0·5 M $NaOTs$-^{35}S	5·0	4·9	2·5	2·6	0·50	0·53	7·7	7·4
Formolysis[b]	None	43·0	43·6	2·7	2·6	0·06	0·06		
	0·05 M $LiClO_4$	44·7	46·1	2·7	2·8	0·06	0·06		
	0·5 M $LiClO_4$	50·7	50·0	2·9	2·7	0·06	0·05		
	0·5 M $NaOTs$-^{35}S	44·5	41·6	4·6	4·9	0·10	0·12	6·5	6·0

[a] 0·5 Mole of 2-phenyl-1-^{14}C-ethyl *p*-toluenesulfonate and 0·5 mole of potassium acetate per liter of acetic acid.
[b] 0·5 Mole of 2-phenyl-1-^{14}C-ethyl *p*-toluenesulfonate and 0·5 mole of potassium formate per liter of formic acid.
[c] Besides potassium acetate or potassium formate.

the formation of hydrocinnamic acid, and secondly, the hydrocinnamic acid oxidizes much more readily than 2-phenylethyl iodide.

Acetolysis and formolysis of 0·5 M solutions of I were carried out at reflux temperature in the presence of equimolar quantities of potassium acetate and potassium formate, respectively. In some experiments, other salts added included 0·1 or 1·0 molar equivalent of lithium perchlorate or 1·0 molar equivalent of sodium *p*-toluene-^{35}S-sulfonate. The acetolyses were interrupted after 30 min of refluxing and the formolyses after 20 minutes of refluxing. Under these conditions, 2-phenylethyl *p*-toluenesulfonate (I_r) recovered from the reaction mixtures ranged between 50 and 60 per cent and between 40 and 50 per cent, respectively, for the acetolyses and formolyses. Samples of the recovered sulfonate, I_r, were degraded to benzoic acid as indicated earlier. The products of solvolysis, 2-phenylethyl acetate or 2-phenylethyl formate, were also oxidized to benzoic acid with potassium permanganate. In each case, the radioactivity in the benzoic acid was a measure of the rearrangement of the ^{14}C-labeled atoms from the C-1 to the C-2 positions of the 2-phenylethyl group. For example, for run no. 1 in the acetolysis with no added salt other than potassium acetate, the radioactivity, on a molar basis, for the hydrocinnamic acid derived from I was 14,394 c.p.m. The benzoic acid derived from the recovered sulfonate I_r and from the reaction product contained, respectively, 294 and 687 c.p.m. of radioactivity on a molar basis. Thus the rearrangement in the recovered 2-phenylethyl *p*-toluenesulfonate was $294/14394 \times 100 = 2{\cdot}0\%$, and the rearrangement in the reaction product, 2-phenylethyl acetate, was $687/14394 \times 100 = 4{\cdot}8\%$. The extents of such rearrangements for all solvolysis runs are summarized in Table 1.

For the solvolyses in the presence of sodium *p*-toluene-^{35}S-sulfonate, besides determinations of ^{14}C rearrangements, the exchange or incorporation of ^{35}S into the recovered 2-phenylethyl *p*-toluenesulfonate (I_r) were measured. Thus for acetolysis run no. 1 carried out in the presence of an equimolar amount of ^{35}S-labeled sodium *p*-toluenesulfonate, the specific activity of the barium sulfate derived from the added sodium *p*-toluene-^{35}S-sulfonate and from the recovered sulfonate I_r were, respectively, 3456 and 266 c.p.m. The ^{35}S incorporated into the recovered 2-phenylethyl *p*-toluenesulfonate, therefore, equals $266/3456 \times 100 = 7{\cdot}7\%$. The results on the ^{35}S incorporation into I_r from both acetolysis and formolysis are also included in Table 1.

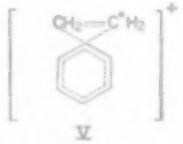
DISCUSSIONS

The possible processes for return from ionic intermediates to covalent bonding during solvolysis have been extensively discussed by Winstein *et al.*[3,4] The following sequence of ionization-dissociation has been postulated:

$$\underset{\text{II}}{RX} \rightleftarrows \underset{\text{III}}{R^+X^-} \rightleftarrows R^+ \| X^- \rightleftarrows \underset{\text{IV}}{R^+ + X^-}$$

The species represented by II is termed an intimate ion-pair, III a solvent separated ion-pair and IV dissociated ions. In the intimate ion-pair, no solvent molecule intervenes between the ions. In the solvent separated ion-pair, the solvation shells of the ions are believed to overlap.[5] Return to covalent bonding can occur from II, III or IV. It was suggested[3] that return from II be called "internal return", and return from III or IV "external return". More specifically, return from III may be termed "external ion-pair return" and return from IV "external ion return". It is of interest to bear these postulated processes in mind in the discussion of the present results.

With reference to the results tabulated in Table 1, the fact that there is rearrangement of the ^{14}C-labeled atoms from the C-1 to C-2 positions in every sample of 2-phenylethyl *p*-toluenesulfonate (I_r) recovered from partially solvolyzed reaction mixtures definitely indicated some return to covalent bonding involving an intermediate ethylphenonium ion (V) or its equivalent. That the rearrangements in



V

most of the recovered samples of sulfonate I_r are of the order of 2 per cent is merely a matter of coincidence. It did not arise from the use of a rearranged starting material since degradation of the starting material, I, has shown that it has no activity on carbon-2. Because anchimeric assistance through phenyl participation and anchimerically unassisted solvolysis both contribute to the acetolysis and formolysis of I[1,2,6] and because S_N2 displacement by the conjugate base of the solvent may also be important, as a qualitative indication of the magnitude of the return process from ionic intermediates, a rearrangement ratio, obtained from division of the percentage

[3] S. Winstein, E. Clippinger, A. H. Fainberg, R. Heck and G. C. Robinson, *J. Amer. Chem. Soc.* **78**, 328 (1956).
[4] S. Winstein and G. C. Robinson, *J. Amer. Chem. Soc.* **80**, 169 (1958).
[5] E. Grunwald, *Analyt. Chem.* **26**, 1696 (1954).
[6] S. Winstein and R. Heck, *J. Amer. Chem. Soc.* **78**, 4801 (1956).

rearrangement in the recovered sulfonate I_r by the percentage rearrangement in the corresponding reaction product, is more significant than the percentage rearrangement in I_r as such. These rearrangement ratios are tabulated in Table 1.

For the acetolysis and formolysis of I with no added salt other than potassium acetate or potassium formate, the extent of isotope position rearrangement in the recovered sulfonate, I_r, was slightly higher for formolysis than for acetolysis. However, the rearrangement ratio for acetolysis averaged 0·42 while this ratio for formolysis was only 0·06. These ratios indicate that in the acetolysis, the return process or processes involving the ethylphenonium ion (V) averaged 42 per cent as much as the formation of reaction product, 2-phenylethyl acetate, through V. On the other hand, the return process or processes through V during formolysis was only 6 per cent as much as the formation of 2-phenylethyl formate through V. This is what one would expect since the increase in ionizing power of formic acid over acetic acid would tend to facilitate further solvolysis and relatively retard the return step.[4,7]

With added lithium perchlorate, it is evident that salt-promoted ionization[3,4] occurred as the extent of isotope position rearrangements in the reaction products increased with increasing amounts of this added salt. The contribution from such an increase in ionization with phenyl participation to the overall solvolysis would account for at least in part, if not entirely, the increase in acetolysis rate of 2-phenylethyl *p*-toluenesulfonate attributed to the "normal salt effect" of added lithium perchlorate.[8] The presence of lithium perchlorate is expected to reduce the extent of the return process or processes, possibly through irreversible formation of a carbonium perchlorate ion-pair which will only give rise to reaction product and thereby preventing some of the carbonium ions from possible returns to covalent bonding.[4,7] In the acetolysis, the presence of an equimolar quantity of lithium perchlorate decreased the rearrangement ratio from about 0·4 to about 0·2, in agreement with expectation.

The data discussed so far do not differentiate the types of return processes involved because the arguments presented can be applied to both external and internal returns. For the solvolysis of I in the presence of sodium *p*-toluene-^{35}S-sulfonate, a more detailed dissection of the return processes is possible. The incorporation of ^{35}S in the recovered sulfonate I_r may be accounted for by the exchange for added *p*-toluenesulfonate anion in the return from ionic intermediates to covalent bonding, or by a bimolecular displacement reaction between added *p*-toluenesulfonate anion and I, or both. The ^{14}C rearrangement in the recovered sulfonate I_r must arise from return involving ionic intermediates; the bimolecular displacement between *p*-toluenesulfonate anion and I will not contribute to ^{14}C rearrangement in I_r. For the present system, especially in the acetolysis, it is very likely that some of the ^{35}S found in I_r was derived from such a bimolecular displacement since considerable bimolecular reaction between 2-phenylethyl *p*-toluenesulfonate and acetate anion was noted during acetolysis.[9] Even if one were allowed to neglect the incorporation of ^{35}S into I_r through bimolecular displacement, the presence of ^{35}S in I_r is not a definitive criterion for a differentiation between external and internal returns because it may be possible to have exchange of *p*-toluenesulfonate anion with ionic intermediates II, III

[7] A. Streitwieser, Jr., *Chem. Rev.* **56**, 571 (1956).
[8] A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.* **78**, 2767 (1956).
[9] S. Winstein, C. R. Lindegren, H. Marshall, and L. L. Ingram, *J. Amer. Chem. Soc.* **75**, 147 (1953).

VOL. 7 1959

or IV. On the other hand, if the results were to show an absence of ^{35}S in I_r while I_r still shows ^{14}C rearrangement, then such observations would be decisive evidence for internal return, namely return from intimate ion-pair II. However, such results were not observed.

Considering the actual experimental data given in Table 1, the interpretation of the amount of ^{35}S in I_r in conjunction with the magnitude of ^{14}C rearrangement in I_r can lead to some interesting conclusions. Take, for example, formolysis runs. No. 1 and 2 in the presence of an equimolar quantity of sodium *p*-toluene-^{35}S-sulfonate, the ^{14}C rearrangements in I_r were 4·6 per cent and 4·9 per cent, respectively. If this rearrangement were to arise entirely from return involving carbonium ion V and the added *p*-toluene-^{35}S-sulfonate anion, the incorporation of ^{35}S into I_r would have to be $2 \times 4{\cdot}6 = 9{\cdot}2\%$[10] and $2 \times 4{\cdot}9 = 9{\cdot}8\%$[10] of the ^{35}S-labeled sulfonate added. However, allowance should be made for the dilution of the added *p*-toluene-^{35}S-sulfonate anions by the *p*-toluenesulfonate anions formed during the reaction. Under the experimental condition employed, an estimated correction factor of 0·8 would have to be applied for reactions interrupted at 50 per cent completion. The expected incorporation of ^{35}S into I_r for the two formolysis runs would be $0{\cdot}8 \times 9{\cdot}2 = 7{\cdot}4\%$ and $0{\cdot}8 \times 9{\cdot}8 = 7{\cdot}8\%$ if only external return were operative and if bimolecular displacement between I and *p*-toluene-^{35}S-sulfonate anion were negligible. Actually, the percentage ^{35}S incorporated in I_r was less, namely, 6·5 per cent and 6·0 per cent for the two runs, indicating that at least some of the *p*-toluenesulfonate anions involved in the return to give isotopically rearranged I_r were derived from an intramolecular process. In other words, there is definitely some internal return from an intimate ion-pair in the formolysis of I.

To account for the incorporating of ^{35}S in I_r from formolysis, one may assume the occurrence of only bimolecular displacement between *p*-toluene-^{35}S-sulfonate anion and I without postulating any external return. However, very probably, this is not the case as external return may be regarded as playing a definite role from the following considerations. Comparing the ^{14}C rearrangements in the reaction product and in the recovered I_r from formolysis runs with and without added sodium *p*-toluene-^{35}S-sulfonate, it can be seen that the extent of salt-promoted ionization due to added sodium *p*-toluenesulfonate is small, if any. However, the extent of rearrangements in the recovered I_r is increased considerably by the presence of sodium *p*-toluenesulfonate. Thus the rearrangement ratios rose from 0·06 to an average of 0·11 for formolysis without and with added sodium *p*-toluenesulfonate. These ratios indicate that the presence of added *p*-toluenesulfonate anion increased the fraction of carbonium ions (V) undergoing return to covalent bonding. Such an effect is reminiscent of the "mass-law effect" of added common ions[11] and thus is indicative of the occurrence of external return. One may, therefore, reasonably conclude that in the formolysis of I, both internal return and external ion return take place.

For the acetolysis of I in the presence of an equimolar quantity of sodium *p*-toluene-^{35}S-sulfonate, the results are not as clear cut as those from formolysis. The fact that the percentage ^{35}S in the recovered sulfonate I_r was more than twice the percentage ^{14}C rearrangement in I_r (see Table 1) appears to indicate that it may not

[10] If a bimolecular displacement between I and *p*-toluene-^{35}S-sulfonate anion occurs, the ^{35}S incorporation would have to be still higher.

[11] L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold and N. A. Taher, *J. Chem. Soc.* 979 (1940).

be necessary to postulate the occurrence of internal return in the acetolysis. However, a substantial part of the ^{35}S in I_r recovered from acetolysis may be derived from bimolecular displacement between *p*-toluene-^{35}S-sulfonate and I, though the present data cannot show what fraction of the ^{35}S in I_r should be attributed to this source. Actually, one should expect, by analogy with formolysis, that both internal and external returns may be involved in the acetolysis of I.

Considerable kinetic data on the acetolysis of 2-phenylethyl *p*-toluenesulfonate have been reported by Winstein *et al.*[6,8,9] It is of interest to note that in the acetolysis of certain systems, these workers observed a "special salt effect" characterized by a rather large increase in rate with the addition of small amounts of lithium perchlorate and that such a special salt effect was not observed in the acetolysis of 2-phenylethyl *p*-toluenesulfonate.[8] The occurrence of this special salt effect has been attributed to a suppression of external ion-pair return, or the suppression of return from solvent separated ion-pair III.[4] For a system which does not show the special salt effect but does show evidence of a return process, the return is then inferred to be internal return from intimate ion-pair II.[4] Since acetolysis of I would not give an observable special salt effect,[8] one may then argue that only internal return is operative during acetolysis of I. However, since the contribution to the overall acetolysis reaction of I by the ionic process involving carbonium ion V or its equivalent amounts to only about 10 per cent,[12] under such circumstances, it is uncertain whether the absence of observable special salt effect would have the same significance as in systems with more stable carbonium ions. The quite sensitive isotope position rearrangement data given in Table 1 show an increase in the rearrangement ratios of from about 0·4 to about 0·5 for acetolysis of I in the absence and in the presence of added sodium *p*-toluenesulfonate. Such results again indicate a greater fraction of V undergoing return when the common *p*-toluenesulfonate anion is present. It is, therefore, very likely that during acetolysis as well as formolysis of I, returns to covalent bonding involve both external and internal returns.

EXPERIMENTAL

The preparation of 2-phenyl-1-^{14}C-ethyl *p*-toluenesulfonate (I), the solvolyses of I, and the degradation of the solvolyses products have been described previously.[1] In the present work, acetolyses or formolyses of I, with or without added lithium perchlorate or sodium *p*-toluene-^{35}S-sulfonate, were interrupted before completion and the reaction products as well as the "unreacted" 2-phenylethyl *p*-toluenesulfonate were recovered for degradation. A typical run, that of a formolysis in the presence of an equimolar quantity of sodium *p*-toluene-^{35}S-sulfonate, is given below to illustrate the present experimental procedures.

Sodium p-*toluene*-^{35}S-*sulfonate*. *p*-Toluene-^{35}S-sulfonic acid was prepared by sulfonation of toluene with concentrated sulfuric acid containing ^{35}S. The method used was as described by Lucas and Pressman.[13] The product obtained, after recrystallization from dioxane and petroleum ether, melted at 103–104°. A diethyl ether solution of this *p*-toluene-^{35}S-sulfonic acid and 2-phenylethyl *p*-toluene-sulfonate showed no exchange of ^{35}S after standing at room temp for 1 week. The sodium *p*-toluene-^{35}S-sulfonate was prepared from the acid by neutralization with sodium carbonate followed by complete removal of the excess water.

Formolysis in the presence of sodium p-*toluene*-^{35}S-*sulfonate*. A mixture of 4·00 g (0·0145 mole) 2-phenyl-1-^{14}C-ethyl *p*-toluenesulfonate, 2·82 g (0·0145 mole) sodium *p*-toluene-^{35}S-sulfonate, and 1·22 g (0·0145 mole) potassium formate in 29 ml anhydrous formic acid (m.p. 8·3° ± 0·1°) was refluxed for 20 min. The resulting mixture was poured onto crushed ice and then extracted 3 times

[12] From the ^{14}C rearrangement of about 5% in the reaction product, 2-phenylethyl acetate.[1]

[13] H. J. Lucas and D. Pressman, *Principles and Practice in Organic Chemistry* p. 342. John Wiley, New York (1949).

with 40 ml portions ether. The combined extract was washed successively with water, dilute sodium carbonate solution and again with water. The washed extract, after drying over magnesium sulfate, was evaporated to about 5 ml. Low boiling petroleum ether was then added to induce crystallization of the "unreacted" 2-phenylethyl *p*-toluenesulfonate. After cooling in a refrigerator at −10° overnight, the crystals obtained weighed 2·1 g. Two additional recrystallizations from ether and petroleum ether gave a product with a m.p. of 39–40°. (lit[9,14] m.p. 35·5–36·5; 39–40°).

The combined mother liquor and washings from the first crystallization of the recovered 2-phenylethyl *p*-toluenesulfonate was distilled to remove the solvents. Vacuum distillation of the residue yielded 0·81 g 2-phenylethyl formate, b.p. 60–62° at 1·2 mm (lit.[15] b.p. 73–75° at 3 mm).

2-Phenylethyl iodide and sodium p-*toluenesulfonate from the recovered 2-phenylethyl* p-*toluenesulfonate.* A mixture of 1·65 g (0·0060 mole) of the recovered 2-phenylethyl *p*-toluenesulfonate and 1·08 g (0·0072 mole) anhydrous sodium iodide in 55 ml reagent grade acetone was refluxed for 3·5 hr. The sodium *p*-toluenesulfonate, which appeared as an insoluble product during the reaction, was filtered off and thoroughly washed with acetone. It weighed 1·06 g (91%) and it was saved for ^{35}S assay.

The combined filtrate and washings after the removal of the sodium *p*-toluenesulfonate was evaporated to approximately 5 ml and then diluted with 50 ml petroleum ether. The resulting solution was washed with 10 ml 1% sodium bisulfite solution and then with two 20 ml portions water. After drying over magnesium sulfate, the solvent was removed and the residue distilled under reduced pressure to give 1·22 g (88%) 2-phenylethyl iodide, b.p. 67–68° at 1·2 mm (lit.[16] b.p. 114–116° at 12 mm).

Hydrocinnamic acid. A solution of 1·58 g (0·0069 mole) 2-phenylethyl iodide in 8 ml anhydrous ether was added dropwise over a period of 10 min to a stirred mixture of 0·50 g (0·021 mole) reagent grade magnesium dust in 8 ml of anhydrous ether. The magnesium had been previously activated by the addition of a few small drops of ethyl bromide. Two to three minutes after the addition of the 2-phenylethyl iodide was completed, the Grignard solution was pipetted from the excess magnesium and put into a 250 ml Erlenmeyer flask cooled at about −20°. A slow stream of dry carbon dioxide was bubbled into the Grignard solution for 15 min. Cold, dil HCl was then added until the mixture was decidedly acidic. Any diethyl ether remaining was removed by a current of air, leaving behind the aqueous layer containing some oil which crystallized on cooling. The yellowish crystals were filtered off, dissolved in a few ml dil NaoH and then washed 3 times with 20 ml portions ether. Acidification of the aqueous solution resulted in a crystalline product which after air drying weighed 0·66 g (64%). Recrystallized twice from petroleum ether, it melted at 48°. (lit.[17b] m.p. 47°, 48·5°).

The procedure described above gave the best yields of hydrocinnamic acid. Refluxing the Grignard reaction mixture during or after the addition of 2-phenylethyl iodide tended to cause the formation of 1,4-diphenylbutane, m.p. 51–52° (lit.[17a] m.p. 52°).

Benzoic acid from hydrocinnamic acid. A mixture of 200 mg hydrocinnamic acid, 1·5 g potassium permanganate and 1·0 g sodium hydroxide in 15 ml water was heated on a steam bath for 3 hr. The reaction mixture was then decolorized by addition of sodium bisulfite and dil HCl. Chilling the resulting solution and collecting the crystals formed gave benzoic acid in approximately 90% yield. The product was recrystallized several times from water and finally sublimed before being assayed for ^{14}C activity.

Radioactivity assays. ^{14}C activities were assayed by converting all compounds to barium carbonate and counting it as infinitely thick samples of constant geometry in a gas flow Geiger counter. Specific activity in c.p.m. on a molar basis was obtained by correcting for the presence of non-labeled carbon atoms in a given compound by multiplying the observed activity with the number of carbons per molecule in that compound.[18]

^{35}S activities were assayed by converting the S-containing compounds to sulfate in a Parr bomb calorimeter and counting the sulfate as infinitely thick samples of barium sulfate.

Acknowledgement—The financial support given by the National Research Council of Canada is gratefully acknowledged.

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VOL.
7
1959

NEW HETEROAROMATIC COMPOUNDS—IV[1]

THE NITRATION AND CHLORINATION OF 10-METHYL-10:9-BORAZAROPHENANTHRENE

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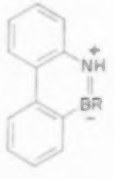
(*Received* 14 *April* 1959)

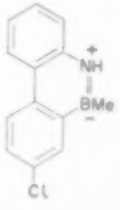
Abstract—10-Methyl- and 10-hydroxy-10:9-borazarophenanthrene have been nitrated with nitric acid in acetic anhydride, and the former compound has been chlorinated with chlorine in acetic acid; the products have been oriented and the proportions of isomers determined quantitatively. The results are shown to be in general agreement with the predictions of MO theory, attack taking place in the 6- and 8-positions. A method for degrading such boron compounds is described, and also the synthesis of 2-, 6-, and 8-chloro-10-methyl-10:9-borazarophenanthrenes as reference compounds. The 6- and 8-amino derivatives of 10-methyl and 10-hydroxy-10:9-borazarophenanthrene have been prepared by reduction of the corresponding nitro derivatives.

IN a recent paper[1] we described the preparation of various derivatives (I) of the new heterocyclic system, 10:9-borazarophenanthrene (I; R = H). The general properties of these compounds indicated their close resemblance to the corresponding isoconjugate derivatives of phenanthrene; we concluded that they are aromatic, and so best represented by the classical structure (I).

In support of this we have now found that the 10-methyl and 10-hydroxy derivatives (I; R = Me, OH) readily undergo nitration or chlorination, without appreciable dealkylation or fission of the boron–nitrogen bond. In view of the theoretical interest of these reactions we have studied them in some detail and determined the orientation of the products formed.



I



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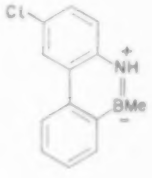
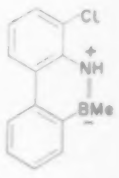


III



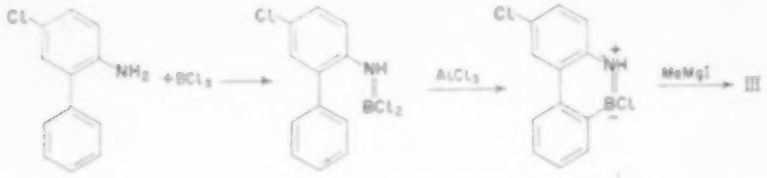
IV

Chlorination of 10-methyl-10:9-borazarophenanthrene (I; R = Me) with one molar equivalent of chlorine in acetic acid gave a mixture of chlorination products in 81 per cent yield. This mixture was separated into two components by chromatography. The main component (A) analysed as a chloro derivative of I (R = Me); its orientation was determined by synthesis and degradation.

It seemed likely on theoretical grounds (see below) that (A) would be 2-, 6-, or

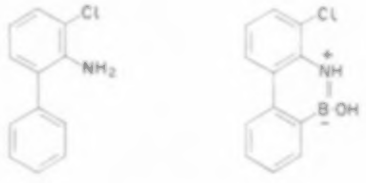
[1] Dewar, Kubba and Pettit, *J. Chem. Soc.* 3073 (1958).

8-chloro-10-methyl-10:9-borazarophenanthrene—i.e. II, III, or IV. These three compounds were synthesized by the method previously described.[1]



Their U.V. spectra are shown in Fig. 1. Comparison showed A to be the 8-chloro isomer (IV).

Although derivatives of I are unchanged by boiling with alkali or concentrated hydrochloric acid, we found that they could be degraded in good yield to derivatives of 2-aminodiphenyl and boric acid by treatment with cold concentrated sulphuric acid, a reaction analogous to the well-known deboronation of arylboronic acids. Treated in this way, A gave 2-amino-3-chlorodiphenyl (V), confirming it to be IV.



V VI

The second compound (B), formed in very small amount, was not identified. Its U.V. spectrum resembled closely that of 10-hydroxy-10:9-borazarophenanthrene (Fig. 2); analogy with nitration (see below) suggests that it was probably 8-chloro-10-hydroxy-10:9-borazarophenanthrene (VI). Only one analysis could be carried out, and that gave an apparently erratic result for carbon; carbon analyses for boron compounds are frequently erratic.

The nitration of 10-methyl-10:9-borazarophenanthrene (I; R = Me) was carried out with nitric acid in cold acetic anhydride; a mixture of nitro compounds was obtained in 78 per cent yield. Chromatography separated this into two main components (C), (D), and a minor component (E). All three formed orange-yellow crystalline solids. The U.V. spectra of C and D are shown in Fig. 3; that of E is shown later (Fig. 4).

Attempts were first made to synthesize the three nitro compounds corresponding to II, III, and IV from the appropriate nitroaminodiphenyls; the amines reacted with boron trichloride, but the products could not be cyclized.

Attempts were then made to convert the nitration products to the corresponding chloro derivatives. Reduction with hydrazine hydrate over palladized charcoal gave the three amines in almost theoretical yield, but attempts to convert them to the chloro compounds by the Sandmeyer reaction failed.

Compounds C and D, which analysed well as nitro derivatives of 10-methyl-10:9-borazarophenanthrene, were then degraded with cold concentrated sulphuric acid; C gave 2-amino-3-nitrodiphenyl (VII), while D gave 2-amino-5-nitrodiphenyl (VIII).

VOL. 7 1959

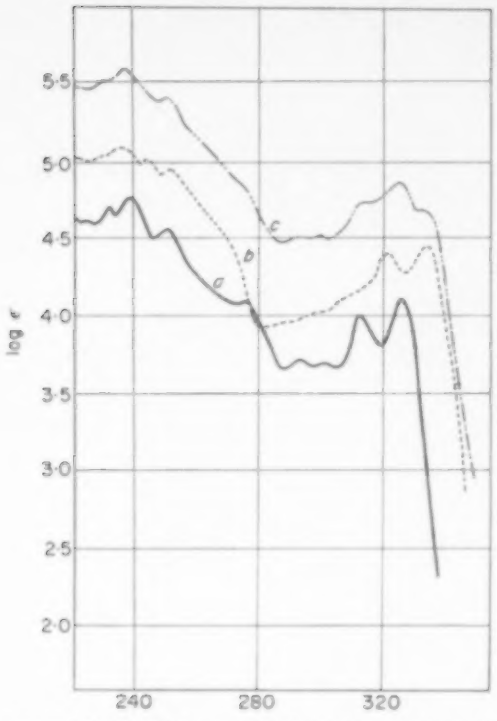


FIG. 1. U.V. spectra of (a) 2-, (b) 6-, and (c) 8-chloro-10-methyl-10:9-borazarophenanthrene. The log ϵ scale applies to (a); the curves for (b) and (c) are displaced by 0·5 and 1·0 respectively to avoid confusion.

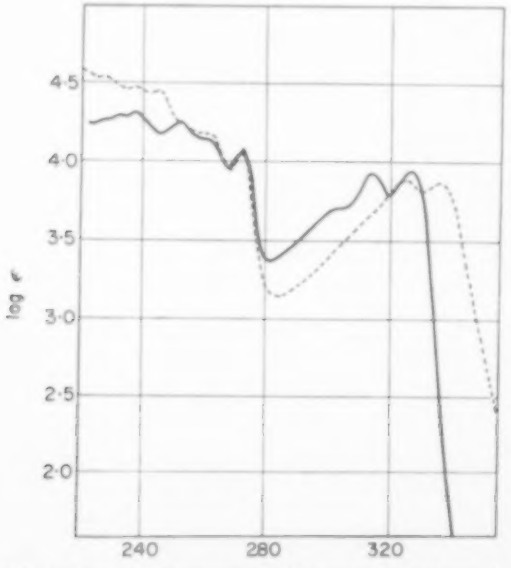
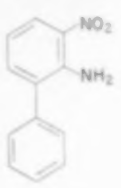
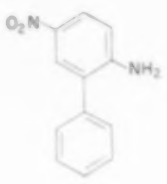


FIG. 2. U.V. spectra of 10-hydroxy-10:9-borazarophenanthrene (———) and the unidentified chlorination product (- - - - - -).

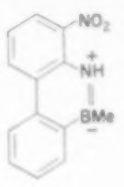
Therefore C was formulated as 8-nitro-10-methyl-10:9-borazarophenanthrene (IX), and D as 6-nitro-10-methyl-10:9-borazarophenanthrene (X).



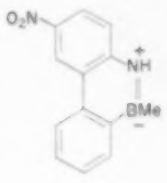
VII



VIII



IX



X

The third component (E) presented difficulties, since at first it gave erratic results on analysis. However, the corresponding amine analysed well as an aminohydroxyborazarophenanthrene, and the I.R. spectrum of E showed it to contain both NH and

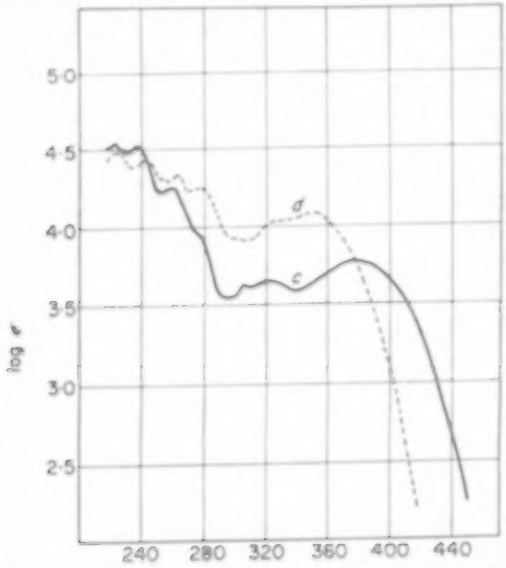
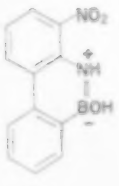
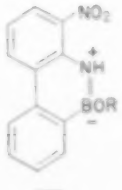


FIG. 3. Spectra of 8-nitro-10-methyl-10:9-borazarophenanthrene (C) (———) and of 6-nitro-10-methyl-10:9-borazarophenanthrene (D) (· · · ·).

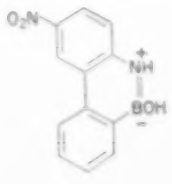
OH groups. Moreover, E was degraded by cold concentrated sulphuric acid to VII. We therefore formulated E as 8-nitro-10-hydroxy-10:9-borazarophenanthrene (XI).



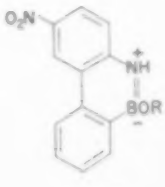
XI



XII



XIII



XIV

This structure was confirmed in two ways. First, it was noticed that E was converted to the corresponding methyl and ethyl ethers (XII; R = Me, Et) merely

by recrystallization from the corresponding alcohols, and that the ethers were hydrolysed on recrystallization from carbon tetrachloride (presumably by traces of water dissolved in the solvent or adsorbed on the surface of the glass vessels used). It is well known that esters of boric acids are formed and hydrolysed with exceptional ease.

Secondly, we obtained by nitrating 10-hydroxy-10:9-borazarophenanthrene a mixture of mononitro derivatives, separated into two components by extraction with

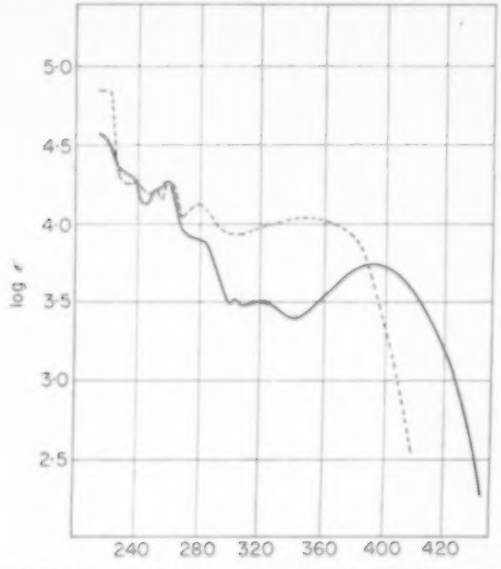
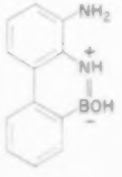


FIG. 4. U.V. spectra of 8-nitro- (———) and 6-nitro(· · · · ·)-10-hydroxy-10:9-borazarophenanthrene.

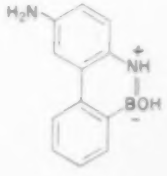
carbon tetrachloride. The soluble component was identical with E, which must therefore be a nitrohydroxyborazarophenanthrene. The insoluble component also analysed as a nitrohydroxyborazarophenanthrene, and it was degraded to VIII by cold concentrated sulphuric acid. It was therefore formulated as 6-nitro-10-hydroxy-10:9-borazarophenanthrene (XIII). Like XI, it was converted to ethers (XIV; R = Me, Et) by crystallization from methanol or ethanol.

The U.V. spectra of XI and XIII are shown in Fig. 4.

Both XI and XIII were reduced by hydrazine hydrate over palladized charcoal to the corresponding amines XV and XVI. The UV spectra of the 8- and 6-amino derivatives of 10-methyl and 10-hydroxy-10:9-borazarophenanthrene are shown in Figs. 5 and 6.



XV



XVI

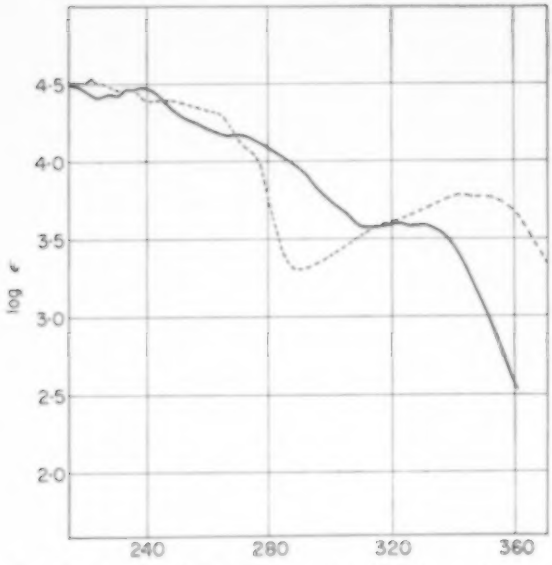


FIG. 5. U.V. spectra of 8- (————) and 6- (· · · · ·)-amino-10-methyl-10:9-borazarophenanthrene.

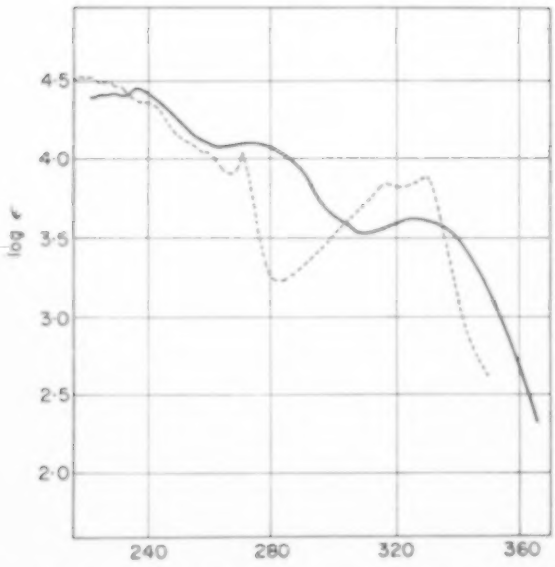


FIG. 6. U.V. spectra of 8- (———) and 6- (· · · ·)-amino-10-hydroxy-10:9-borazarophenanthrene.

The formation of XI by nitration of 10-methyl-10:9-borazarophenanthrene involves demethylation; two lines of evidence suggest that demethylation follows nitration. First, we were unable to detect any XIII in the nitration product, although nitration of 10-hydroxy-10:9-borazarophenanthrene gave comparable amounts of XI and XIII; secondly, if the nitration mixture were allowed to stand for a longer period before hydrolysis, the amount of XI in the product increased and the amount of IX decreased. Presumably, the same thing happens in the chlorination of I; (R = Me), VI being formed by oxidation of IV.

VOL. 7 1959

TABLE 1. PROPORTIONS OF ISOMERS IN SUBSTITUTION REACTION OF BORAZAROPHENANTHRENE DERIVATIVES

Reaction	6-substitution	8-substitution
Chlorination of (I; R = Me)	0	100
Nitration of (I; R = Me)	34	66
Nitration of (I; R = OH)	33·5	66·5

The proportions of isomers formed in the various reactions is listed in Table 1; the proportion of 8-nitro-10-methyl-10:9-borazarophenanthrene quoted is the sum of the relative yields of IX and XI, since XI is apparently formed by a secondary reaction from IX.

Discussion. Theoretical predictions of orientation in aromatic substitution reactions can be made at various levels of sophistication. In the present state of knowledge a suitable compromise seems to be the simplified MO treatment developed by Longuet-Higgins[2] and by one of us[3] some years ago; this has been shown[4] to account well for the products formed in a variety of substitution reactions of polycyclic aromatic hydrocarbons and heterocycles.

In this treatment, the activation energy for substitution at a given position in a heterocycle is divided into two parts; the first is the activation energy for substitution at the corresponding position in the isoconjugate hydrocarbon; the second measures the modifying effect of the heteroatoms.

Substitution in phenanthrene occurs predominantly[4] in the 9-, 1-, and 3-positions; the 1-, 3-, 6-, and 8-positions in 10:9-borazarophenanthrene should therefore be inherently the more reactive. Nitrogen, being more electronegative than carbon, should deactivate positions of opposite parity to itself;[2] the 9-aza-group should therefore selectively deactivate the 1-, 3-, 5-, and 7-positions. Boron, being less electronegative than carbon, should selectively activate the positions of opposite parity to itself—i.e. the 2-, 4-, 6-, and 8-positions. One would therefore expect substitution in 10:9-borazarophenanthrene to occur predominantly in the 6- and 8-positions—in agreement with our observations (Table 1). These relations are indicated in Fig. 7.

[2] Longuet-Higgins, *J. Chem. Phys.* **18**, 265, 275, 283 (1950).
[3] Dewar, *J. Amer. Chem. Soc.* **74**, 3341, 3345, 3350, 3353, 3355, 3357 (1952).
[4] Dewar and Maitlis, *J. Chem. Soc.* 2251 (1957).

Predictions of this kind can be put on a semiquantitative basis.[2,3,4] Table 2 lists the relative activation energies so predicted[4] for substitution in 10:9-borazarophenanthrene. The first term gives the activation energy for substitution at the corresponding position in phenanthrene in terms of the carbon–carbon resonance integral β; the second term represents the effect of the nitrogen atom (coulomb term α_N); the third term represents the effect of boron (coulomb term α_B). The experimental evidence[4] indicates that the 4- and 5-positions in phenanthrene are sterically hindered,

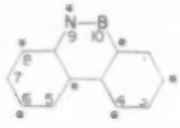


FIG. 7. The starred nitrogen should deactivate positions of opposite parity (i.e. unstarred positions); likewise the unstarred boron should activate the starred positions.

so that their reactivity is close to that of the 2- and 7-positions; the first term has therefore been arbitrarily set equal to that for 2-substitution.

An investigation[4] of nitration in heterocyclic systems suggested that a suitable value for α_N is about 10β; the last column of Table 2 has been calculated on this basis. Boron is less electronegative than carbon; the differences in electronegativity between boron and carbon, and between carbon and nitrogen, are probably comparable. Hence we would expect $\alpha_B \sim -10\beta$; in that case Table 2 indicates that the 6- and 8-positions should be much the most reactive—as observed.

One difficulty remains; on this basis one would expect the 6- and 8-positions to

TABLE 2. CALCULATED RELATIVE ACTIVATION ENERGIES FOR SUBSTITUTION IN 10:9-BORAZAROPHENANTHRENE
(the values (b) are calculated with $\alpha_N = 10\beta$)

Position	AF calc (a)	AF calc (b)
1	$1{\cdot}86\beta + 0{\cdot}138\alpha_N + 0{\cdot}046\alpha_B$	$3{\cdot}24\beta + 0{\cdot}046\alpha_B$
2	$2{\cdot}18\beta + 0{\cdot}016\alpha_N + 0{\cdot}048\alpha_B$	$2{\cdot}34\beta + 0{\cdot}048\alpha_B$
3	$2{\cdot}04\beta + 0{\cdot}167\alpha_N + 0{\cdot}056\alpha_B$	$3{\cdot}71\beta + 0{\cdot}056\alpha_B$
4	$2{\cdot}18\beta + 0{\cdot}013\alpha_N + 0{\cdot}038\alpha_B$	$2{\cdot}31\beta + 0{\cdot}038\alpha_B$
5	$2{\cdot}18\beta + 0{\cdot}038\alpha_N + 0{\cdot}013\alpha_B$	$2{\cdot}56\beta + 0{\cdot}013\alpha_B$
6	$2{\cdot}04\beta + 0{\cdot}056\alpha_N + 0{\cdot}167\alpha_B$	$2{\cdot}60\beta + 0{\cdot}167\alpha_B$
7	$2{\cdot}18\beta + 0{\cdot}048\alpha_N + 0{\cdot}016\alpha_B$	$2{\cdot}66\beta + 0{\cdot}016\alpha_B$
8	$1{\cdot}86\beta + 0{\cdot}046\alpha_N + 0{\cdot}0138\alpha_B$	$2{\cdot}32\beta + 0{\cdot}138\alpha_B$

be of comparable reactivity, whereas in practice the 8-position is the more reactive. However, apart from the uncertainty in the value of α_B, two other factors could be important; the inductive effect of the 9-aza nitrogen on the adjacent 8-position, and the possibility that N-nitration or chlorination may occur, followed by an intramolecular rearrangement to the 8-position.

One further point is of interest; the fact that IX is converted to XI under the conditions of nitration, whereas X appears to be stable. This difference must be due to hydrogen bonding between the nitro and imino groups of IX, though it is not obvious why this should labilize the 10-methyl group to oxidative attack.

VOL. 7 1959

EXPERIMENTAL

(Microanalyses were carried out by the Microanalytical Laboratory, Imperial College, South Kensington, London S.W.7., and by Alfred Bernhardt, Max-Planck-Institut, Mülheim, Germany. Chromatography was carried out with Peter Spence alumina, type H 100/200 mesh).

2-*Chloro*-10-*methyl*-10:9-*borazarophenanthrene*. A solution of 2-amino-4′-chlorodiphenyl (6 g) in dry benzene (50 ml) was added dropwise with vigorous stirring to one of boron trichloride (3·6 g) in dry benzene (200 ml), and the solution was then boiled under reflux for 7 hr. After removing the solvent, anhydrous aluminium chloride (0·3 g) was added, and the mixture heated to 180° for 6 hr. The resulting 2,10-dichloro-10:9-borazarophenanthrene was taken up in dry benzene (100 ml) and a solution of methylmagnesium iodide (from magnesium, 0·9 g, and methyl iodide, 5·2 g) added slowly with vigorous stirring at 0°. The solution was then boiled under reflux for 1 hr and the product isolated by adding dilute acid and ether; evaporation gave 2-*chloro*-10-*methyl*-10:9-*borazarophenanthrene*, which crystallized from light petroleum (b.p. 40–60°) in white needles (4·4 g, 65%), m.p. 98–99° (Found: C, 68·7; H, 4·9; N, 6·3; Cl, 15·5; B, 4·5. $C_{13}H_{11}NClB$ requires: C, 68·6; H, 4·8; N, 6·2; Cl, 15·6; B, 4·8%).

6-*Chloro*-10-*methyl*-10:9-*borazarophenanthrene*. Prepared likewise in 70% overall yield from 2-amino-5-chlorodiphenyl, 6-*chloro*-10-*methyl*-10:9-*borazarophenanthrene* crystallized from light petroleum (b.p. 40–60°) in white needles, m.p. 86–87° (Found: C, 68·6; H, 4·9; N, 6·2; Cl, 15·4; B, 4·7%).

8-*Chloro*-10-*methyl*-10:9-*borazarophenanthrene*. Prepared likewise in 52% overall yield from 2-amino-3-chlorodiphenyl, 8-*chloro*-10-*methyl*-10:9-*borazarophenanthrene* was obtained as an almost colourless liquid, b.p. 170–175°/0·5–0·6 mm. (Found: C, 68·3; H, 4·8; N, 6·0; Cl, 15·7; B, 4·7%).

Chlorination of 10-*methyl*-10:9-*borazarophenanthrene*. Chlorine, prepared from potassium permanganate (4·01 g) and conc. HCl (25·4 ml), was passed slowly into a solution of 10-methyl-10:9-borazarophenanthrene[1] (10 g) in acetic acid (60 ml) at room temp. The solution was then poured into water, neutralized with sodium carbonate, and extracted with ether; evaporation of the ether left a pale brown residue (9·5 g, 81%). A solution of the crude chlorination product (2·35 g) was chromatographed on alumina from benzene, two bands being detected by U.V. fluorescence. The main band gave an oil (1·55 g, 66%), b.p. 170–175°/0·5–0·6 mm. (Found: C, 68·3; H, 4·9; N, 6·0; Cl, 15·8; B, 4·7. $C_{13}H_{11}NClB$ requires: C, 68·6; H, 4·8; N, 6·2; Cl, 15·6; B, 4·8%). The U.V. spectrum was identical with that of 8-chloro-10-methyl-10:9-borazarophenanthrene. Attempts to identify the material (m.p. 182–183°) in the second band were unsuccessful through lack of material. Its U.V. spectrum resembled that of 10-hydroxy-10:9-borazarophenanthrene. Only one analysis could be carried out, and that gave an apparently erratic result for carbon. (Found: C, 64·7; H, 4·2; N, 5·7; Cl, 15·1. $C_{12}H_9ONClB$ requires: C, 62·8; H, 3·9; N, 6·1; Cl, 15·4%).

Degradation of the main chlorination product. The chlorination product (0·5 g) was added to conc H_2SO_4 (20 ml) and left 2 hr at room temp. The solution was then poured into water, basified with sodium hydroxide, and extracted with ether. Removal of the ether left 2-amino-3-chlorodiphenyl (0·25 g, 56%), identified by mixed m.p. of its acetyl derivative.

Nitration of 10-*methyl*-10:9-*borazarophenanthrene*. A solution of nitric acid (*d* 1·5, 4·2 g) in acetic acid (20 ml) was added dropwise with vigorous stirring to one of 10-methyl-10:9-borazarophenanthrene (12·1 g) in acetic anhydride (100 ml), the temp being held at $0 \pm 2°$. After 1 hr the reaction mixture was poured onto water and ice, neutralized with sodium carbonate, and extracted with ether. Evaporation of the dried (Na_2SO_4) extract left a yellowish brown residue. A portion (2·9 g) was chromatographed from benzene on alumina. The first (purple) band was eluted with benzene, giving 8-*nitro*-10-*methyl*-10:9-*borazarophenanthrene* (1·40 g, 48%), which crystallized from benzene–light petroleum in deep yellow needles, m.p. 165–166°. (Found: C, 65·5; H, 4·8; N, 11·7; B, 4·6. $C_{13}H_{11}O_2N_2B$ requires: C, 65·6; H, 4·6; N, 11·7; B, 4·6%). The second (orange) band, eluted with benzene–chloroform, gave 6-*nitro*-10-*methyl*-10:9-*borazarophenanthrene* (0·95 g, 33%), which crystallized from benzene–light petroleum in light yellow needles, m.p. 209–210°. (Found: C, 64·1; H, 4·7; N, 11·3; B, 4·4%). The third (dark orange) band was eluted with chloroform, giving 8-*nitro*-10-*hydroxy*-10:9-*borazarophenanthrene* (0·43 g, 15%) which crystallized from carbon tetrachloride in orange prisms. m.p. 266–267°. (Found: C, 59·8; H, 4,1; N, 11·5; B, 4·2. $C_{12}H_9O_3N_2B$ requires: C, 60·0; H, 3·8; N, 11·6; B, 4·6%). The hydroxy compound gave on recrystallization from ethanol yellow needles of 8-*nitro*-10-*ethoxy*-10:9-*borazarophenanthrene*, m.p. 125–126°. (Found: C, 62·6; H, 4·8; N, 10·6; OEt, 14·5. $C_{14}H_{13}O_3N_2B$ requires: C, 62·7; H, 4·8; N, 10·4; OEt,

16·8%). Recrystallization from methanol likewise gave yellow needles of *8-nitro-10-methoxy-10:9-borazarophenanthrene*, m.p. 155–156°. (Found: C, 61·3; H, 4·5; N, 10·8; OMe, 11·2. $C_{13}H_{11}O_3N_2B$ requires: C, 61·4; H, 4·3; N, 11·0; OMe, 12·2%).

Degradation of 8-nitro-10-methyl-10:9-borazarophenanthrene. The nitro compound (0·50 g) was added to conc H_2SO_4 (20 ml). After 2 hr at room temp the solution was poured onto ice, basified with sodium hydroxide, and extracted with ether. Evaporation of the ether left 2-amino-3-nitrodiphenyl, which crystallized from light petroleum (b.p. 40–60°) in yellow needles (0·35 g, 78%) m.p. and mixed m.p. 46–47°. The diacetyl derivative crystallized from aqueous ethanol, m.p. and mixed m.p. 87–88°. (Found: C, 64·4; H, 4·8; N, 9·6. Calc. for $C_{16}H_{14}O_4N_2$: C, 64·4; H, 4·7; N, 9·4%).

Degradation of 6-nitro-10-methyl-10:9-borazarophenanthrene. The compound (0·40 g), degraded as above, gave 2-amino-5-nitrodiphenyl, which crystallized from aqueous alcohol in yellow needles (0·30 g, 83%), m.p. and mixed m.p. 125–126°.

Nitration of 10-hydroxy-10:9-borazarophenanthrene. To a stirred solution of the hydroxy compound (6·0 g) in acetic anhydride (85 ml) was added dropwise a solution of fuming nitric acid (*d* 1·5; 2·1 g) in acetic anhydride (10 ml), the temp being kept at 0 ± 2°. After 1 hr the reaction mixture was hydrolysed with ice-cooled water, neutralized, and extracted with ether. Evaporation of the dried (Na_2SO_4) extract gave a yellowish brown mixture of nitro compounds (6·5 g, 88%). The mixture (6·5 g) was extracted with hot carbon tetrachloride (6 × 250 ml); concentration of the extract gave orange crystals of 8-nitro-10-hydroxy-10:9-borazarophenanthrene (4·2 g, 65%), m.p. and mixed m.p. 266–267°. Recrystallization from ethanol gave 8-nitro-10-ethoxy-10:9-borazarophenanthrene, m.p. and mixed m.p. 125–126°. The residue from the carbon tetrachloride extraction crystallized from ethanol in yellow needles (2·1 g 33%), m.p. 172–174°, of *6-nitro-10-ethoxy-10:9-borazarophenanthrene* (Found: C, 62·8; H, 4·9; N, 10·5; OEt, 14·8. $C_{14}H_{13}O_3N_2B$ requires: C, 62·7; H, 4·8; N, 10·4; OEt, 16·8%). On standing in air for 24 hr the compound underwent hydrolysis quantitatively to *6-nitro-10-hydroxy-10:9-borazarophenanthrene*, m.p. 360° (decomp), which was virtually insoluble in non-hydroxylic solvents (Found: C, 59·8; H, 3·9; N, 11·5; B, 4·3. $C_{12}H_9O_3N_2B$ requires: C, 60·0; H, 3·8; N, 11·6; B, 4·6%). The hydroxy compound on recrystallization from methanol gave *6-nitro-10-methoxy-10:9-borazarophenanthrene* as yellow needles, m.p. 237–238°. (Found: C, 61·2; H, 4·4; N, 10·9; OMe, 10·9. $C_{13}H_{11}O_3N_2B$ requires: C, 61·4; H, 4·3; N, 11·0; OMe, 12·2%).

Degradation of 8-nitro-10-hydroxy-10:9-borazarophenanthrene. Degradation of the nitrohydroxy compound (0·5 g) gave 2-amino-3-nitrodiphenyl (0·32 g, 72%), m.p. and mixed m.p. 46–47°, m.p. and mixed m.p. of diacetyl derivative, 87–88°.

Degradation of 6-nitro-10-hydroxy-10:9-borazarophenanthrene. Degradation of the compound (0·5 g) gave 2-amino-5-nitrodiphenyl (0·36 g, 80%), m.p. and mixed m.p. 125–126·5°.

8-Amino-10-methyl-10:9-borazarophenanthrene. Hydrazine hydrate (5 ml) was added dropwise to a boiling solution of 8-nitro-10-methyl-10:9-borazarophenanthrene (1 g) in ethanol containing palladized charcoal (0·1 g, of 10%). After 30 min the solution was cooled, filtered, and evaporated to dryness under reduced pressure, leaving *8-amino-10-methyl-10:9-borazarophenanthrene* which crystallized from light petroleum (b.p. 60–80°) in white needles (0·65 g, 76%) m.p. 137–138°. (Found: C, 75·2; H, 6·7; N, 13·3; B, 5·2. $C_{13}H_{13}N_2B$ requires: C, 75·1; H, 6·2; N, 13·4; B, 5·3%).

6-Amino-10-methyl-10:9-borazarophenanthrene. Prepared likewise from the nitro compound in 69% yield, *6-amino-10-methyl-10:9-borazarophenanthrene* crystallized from light petroleum (b.p. 60–80°) in white needles, m.p. 125–126°. (Found: C, 75·2; H, 6·2; N, 13·6; B, 5·3%).

8-Amino-10-hydroxy-10:9-borazarophenanthrene. Prepared likewise in 74% yield, *8-amino-10-hydroxy-10:9-borazarophenanthrene* crystallized from benzene in white granules, m.p. 195–196°. (Found: C, 68·6; H, 5·2; N, 13·2; B, 4·9. $C_{12}H_{11}ON_2B$ requires: C, 68·6; H, 5·2; N, 13·4; B, 5·2%).

6-Amino-10-hydroxy-10:9-borazarophenanthrene. Prepared likewise in 65% yield, *6-amino-10-hydroxy-10:9-borazarophenanthrene* crystallized from benzene in white granules, m.p. 218–220°. (Found: C, 68·6; H, 5·4; N, 13·2; B, 5·0%).

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VOL.
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ZUR KONSTITUTION DER SANDARAKOPIMARSÄURE—II*

ÜBER DIE STERISCHE BEZIEHUNG DER SANDARAKOPIMARSÄURE ZU DEN DEXTROPIMARSÄUREN†

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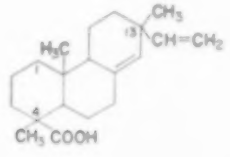
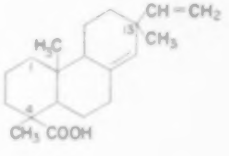
(*Received* 20 *April* 1959)

Zusammenfassung—Durch teilweise Dehydrierung der Sandarakopimarsäure mit Palladium wurde ein flüssiger Kohlenwasserstoff $C_{18}H_{22}$ erhalten. Dieser erwies sich als identisch mit einem schon bekannten, durch die Dehydrierung der Dextropimarsäure gewonnenen Kohlenwasserstoff. Daraus wird geschlossen, dass die Sandarakopimarsäure am Kohlenstoffatom 13 dieselben Substituenten und dieselbe Konfiguration wie die Dextropimarsäure besitzt.

IN unserer früheren Abhandlung über Sandarakopimarsäure[1] haben wir mitgeteilt, dass diese Säure mit der Dextropimarsäure (I), bzw. mit der Isodextropimarsäure (II), nahe verwandt ist. Diese Annahme stützte sich auf das Ergebnis der Dehydrierung der Sandarakopimarsäure mit Selen, wobei das Pimanthren (III) erhalten worden war. Eine weitere Stütze lieferte der Vergleich der I–R–Spektren der Methylester der drei genannten Säuren. Dagegen schlossen die Mischschmelzpunkte der Methylester die Identität der Sandarakopimarsäure mit den Säuren (I) oder (II) aus. Das führte uns zu der Annahme, dass der Unterschied zwischen Sandarakopimarsäure und den Säuren (I) oder (II) in einer abweichen Konfiguration am Kohlenstoffatom 4 besteht.



I



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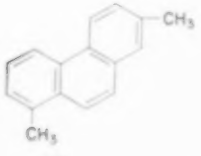
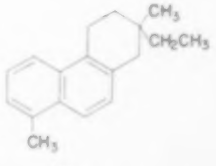


III



IV

* Mitteilung I: F. Petrů u.V. Galik, *Coll. Czech. Chem. Comm.* **18**, 717 (1953).
† Vorläufige Mitteilung: V. Galik, F. Petrů u. J. Kuthan, *Naturwissenschaften* **46**, 322 (1959).
‡ Jetzige Arbeitsstätte: Laboratorium für heterocyklische Verbindungen der Tschechoslowakischen Akademie der Wissenschaften.
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Um diese Annahme weiter zu verfolgen, gingen wir von den, die Dehydrierung der Säuren (I) und (II) betreffenden Angaben von Harris und Sanderson[2] aus, und unterwarfen die Sandarakopimarsäure einer teilweisen Dehydrierung mit Palladium. Wir erhielten ein öliges Produkt, aus welchem chromatographisch zwei Anteile abgetrennt werden konnten. Der erste Anteil war ein flüssiger Kohlenwasserstoff vom $Sdp._{0,1}$ 129–135° (Badtemperatur), $n_D^{20} = 1{,}5789$, und lieferte mit 1,3,5-Trinitrobenzol eine Additionsverbindung vom Schmp. 122–123°, deren Analyse mit der Formel $C_{18}H_{22}$ des Kohlenwasserstoffs im Einklang war. Der zweite, kristalline Anteil konnte als Pimanthren (III) identifiziert werden.

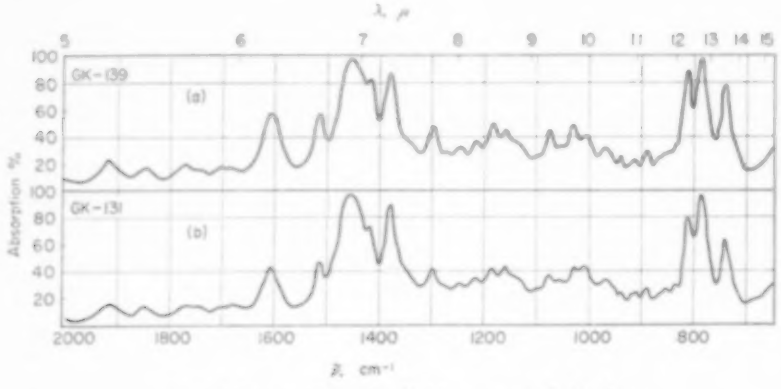

Abb. 1. Infrarot-spektren des Kohlenwasserstoffs $C_{18}H_{22}$
(a) Kohlenwasserstoff aus der Dextropimarsäure + Pd
(b) Kohlenwasserstoff aus der Sandarakopimarsäure + Pd.

Ein Vergleich der Infrarot—spektren und die Mischschmelzpunkte der Additionsverbindungen mit 1,3,5-Trinitrobenzol zeigten die Identität des Kohlenwasserstoffs $C_{18}H_{22}$ mit dem flüssigen Kohlenwasserstoff, der von uns,[1] neben Pimanthren, bei der Dehydrierung der Sandarakopimarsäure mit Selen erhalten worden war.

Harris und Sanderson[2] erhielten jedoch bei der Dehydrierung der Dextropimarsäure mit Palladium einen flüssigen Kohlenwasserstoff $C_{18}H_{22}$ (IV). Bei der Wiederholung der Versuche von Harris und Sanderson konnten wir den von diesen Autoren beschriebenen Kohlenwasserstoff isolieren und seine Identität mit dem von uns aus der Sandarakopimarsäure erhaltenen Kohlenwasserstoff $C_{18}H_{22}$ beweisen. Beide Kohlenwasserstoffe bildeten nämlich mit 1,3,5-Trinitrobenzol Additionsverbindungen vom Schmp. 122–123°, der bei der Mischprobe keine Erniedrigung zeigte. Eine weitere Stütze lieferte der Vergleich der Infrarot-Spektren (vergl. Abb. 1), während das Ultraviolett-spektrum die Identität mit dem Kohlenwasserstoff von Harris und Sanderson ergab (vergl. Abb. 2).

Bei der optischen Untersuchung der Kohlenwasserstoffe $C_{18}H_{22}$ aus der Dextropimarsäure und der Sandarakopimarsäure fanden wir, dass beide Kohlenwasserstoffe optisch aktiv sind, und dass sie denselben (positiven) Drehungssinn zeigen. Daraus kann man schliessen, dass die Konfiguration am Kohlenstoffatom 13 bei der Sandarakopimarsäure die gleiche ist wie bei der Dextropimarsäure, während die Isodextro-

[1] F. Petrů u. V. Galik, *Coll. Czech. Chem. Comm.* **18**, 717 (1953).
[2] G. C. Harris u. T. F. Sanderson, *J. Amer. Chem. Soc.* **70**, 2081 (1948).

pimarsäure an diesem Kohlenstoffatom die umgekehrte Konfiguration besitzt.[2–4] Somit dürfte die Untersuchung der gegenseitigen Beziehung der Sandarakopimarsäure zur Dextropimarsäure in erster Linie die Konfiguration am Kohlenstoffatom 4 betreffen. Unsere Ergebnisse in dieser Richtung werden in einer späteren Veröffentlichung mitgeteilt.

VOL. 7 1959

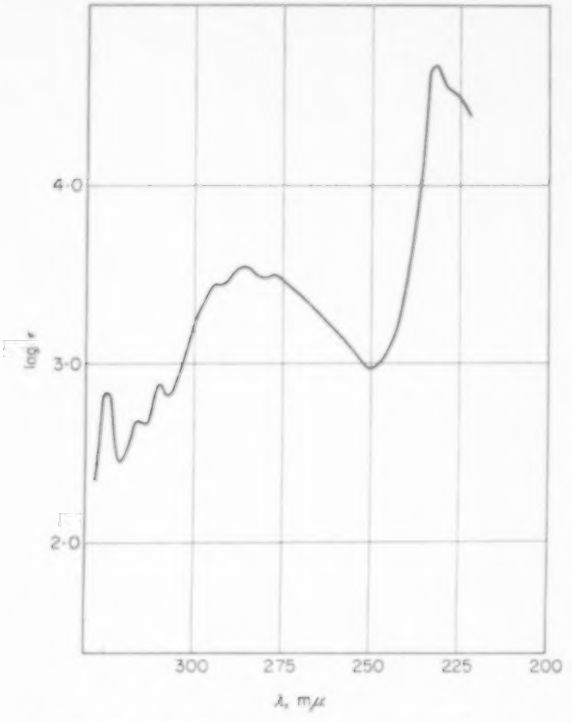

Abb. 2. Ultraviolett-Spektrum des Kohlenwasserstoffs $C_{15}H_{22}$ aus der Sandarakopimarsäure + Pd.

BESCHREIBUNG DER VERSUCHE

Darstellung der Sandarakopimarsäure aus käuflichem Sandarak

Die früher von uns[1] angegebene Vorschrift zur Darstellung der Sandarakopimarsäure wurde folgendermassen abgeändert:

200 g käuflichen Sandaraks wurden mit 800 ml Äther verrieben. Nach dreitägigem Aufbewahren bei Zimmertemperatur wurde die ätherische Lösung abgegossen und mit gasförmigem Ammoniak gesättigt. Der abgeschiedene Niederschlag wurde abgesaugt und mit 100 ml Äther gewaschen. Die vereinigten Filtrate wurden mit insgesamt 500 ml 1-proz. Natronlauge ausgeschüttelt. Die vereinigten alkalischen Auszüge wurden mit verdünnter Essigsäure (1 : 3) bis zur sauren Reaktion versetzt. Der gebildete klebrige Niederschlag wurde mehrmals mit kaltem Wasser dekantiert und schliesslich in 60 ml 5-proz. Natronlauge gelöst. Die entstandene, mit Wasser auf das doppelte Volumen verdünnte Lösung wurde vorsichtig mit 5-proz. Natronlauge bis zur deutlichen alkalischen Reaktion und dem Auftreten einer Trübung versetzt.* Nach mehrstündigem Stehen in der Kälte schied sich das

* Ein Ueberschuss von Alkali hat die Abscheidung eines klebrigen Niederschlags zur Folge.

[5] A. Brossi u. O. Jeger, *Helv. Chim. Acta* **33**, 722 (1950).
[6] O. E. Edwards u. R. Howe, *Chem. & Ind.* 629 (1958).

Natriumsalz der Sandarakopimarsäure als griessförmiger Niederschlag ab. Das Produkt wurde abgenutscht, dreimal aus Wasser umkristallisiert und schliesslich bei 60° in Wasser gelöst. Die Lösung wurde mit Kohlendioxyd gesättigt, der gebildete Niederschlag abgenutscht und aus Äthanol umkristallisiert. Die auf diese Weise gewonnene Sandarakopimarsäure bildete farblose Nadeln vom Schmp. 172° (korr.). Die Ausbeute betrug 1,2 g. Bei der Mischprobe mit dem früher[1] beschriebenen Präparat wurde keine Schmelzpunkterniedrigung beobachtet.

Dehydrierung der Sandarakopimarsäure mit Palladium

Ein Gemisch von 0,55 g Sandarakopimarsäure und 0,3 g 5-proz. Palladiumkohle wurde während 2 Stdn. im milden Kohlendioxydstrom auf 290–310° erhitzt. Nach dem Erkalten wurde das Reaktionsprodukt in 50 ml Petroläther (Sdp. 40–50°) gelöst. Aus der abfiltrierten und getrockneten

TABELLE 1. CHROMATOGRAPHISCHE TRENNUNG DER REAKTIONSPRODUKTE DER DEHYDRIERUNG DER SANDARAKOPIMARSÄURE MIT PALLADIUM

Anteil	Lösungsmittel	Menge in ml	Produkt: Ausbeute g	Beschaffenheit
1	Petroläther	10	—	—
2	Petroläther	10	0,175	farbloses Öl
3	Petroläther	10	0,122	farbloses Öl
4	Petroläther	10	0,024	farbloses Öl
5	Petroläther	10	0,007	farbloses Öl
6	Petroläther	10	0,007	farbloses Öl
7	Petroläther	10	—	—
8	Petroläther-Benzol	10	—	—
9	Petroläther-Benzol	10	0,0005	kristallisierendes Öl
10	Benzol	10	0,002	Kristalle, Schmp. 75–77°
11	Benzol	10	0,011	Kristalle, Schmp. 75–77°
12	Benzol	10	—	—

Lösung wurde das Lösungsmittel durch Destillation entfernt. Der Rückstand, 0,37 g eines farblosen, blau fluoreszierenden Öls, wurde in 5 ml Petroläther gelöst, und die Lösung wurde unter Verwendung von 10 g Aluminiumoxyd (Aktivität I, nach Brockmann) chromatographiert (Tabelle 1).

Die *Fraktion* 2 wurde zweimal aus einem Hickmann-Kolben destilliert. Der Anteil vom $Sdp._{0,1}$ 129–135° (Badtemperatur), $n_D^{20} = 1{,}5789$ (Substanz *A*), wurde zur Aufnahme des Infrarotspektrums (Abb. 1) und zur optischen Untersuchung verwendet.

Die *Fraktionen* 3–4, wurden, in 6 ml Äthanol gelöst, mit einer warmen Lösung von 0,15 g 1,3,5-Trinitrobenzol in 10 ml Äthanol versetzt. Man erhielt 0,2 g Additionsverbindung (Substanz *B*), welche nach dreimaligem Umkristallisieren aus Äthanol bei 122–123° schmolz.

$C_{24}H_{35}N_3O_6$ (451,5): Ber. 63,85% C, 5,58% H, 9,31% N; gef.: 64,09% C, 5,88% H, 9,29% N.

Die *Fraktionen* 10–11 lieferten mit 1,3,5-Trinitrobenzol eine Additionsverbindung vom Schmp. 155–157°, keine Schmelzpunkterniedrigung mit dem aus Pimanthren dargestellten Additionsprodukt.

Dehydrierung der Dextropimarsäure mit Palladium

0,59 g Dextropimarsäure vom Schmp. 211–212° wurden unter den gleichen Bedingungen wie bei der Sandarakopimarsäure mit 0,35 g Palladiumkohle dehydriert. Man erhielt 0,33 g eines farblosen, blau fluoreszierenden Öls, welches, in Petroläther gelöst, auf 10 g Aluminiumoxyd (Aktivität I, nach Brockmann) chromatographiert wurde (Tabelle 2).

Aus den vereinigten *Fraktionen* 2 und 3 wurde durch zweimalige Destillation aus einem Hickmann-Kolben eine Fraktion (Substanz A_1) vom Sdp.$_{0,6}$ 147–148° (Badtemperatur), $n_D^{20} = 1{,}5786$, erhalten, welche zur Aufnahme des Infrarotspektrums (Abb. 1) und des Ultraviolettspektrums (Abb. 2) verwendet wurde. Die aus derselben Substanz dargestellte Additionsverbindung mit 1,3,5-Trinitrobenzol schmolz bei 122–123° und zeigte keine Schmelzpunkterniedrigung mit der Substanz *B*.

TABELLE 2. CHROMATOGRAPHISCHE TRENNUNG DER REAKTIONSPRODUKTE DER DEHYDRIERUNG DER DEXTROPIMARSÄURE MIT PALLADIUM

Anteil	Lösungsmittel	Menge in ml	Produkt: Ausbeute g	Beschaffenheit
1	Petroläther	10	—	—
2	Petroläther	10	0,200	farbloses Öl
3	Petroläther	10	0,080	farbloses Öl
4–6	Petroläther	30	0,020	farbloses Öl
7–8	Petroläther-Benzol	20	—	—
9	Benzol	10	—	—
10–11	Benzol	20	0,03	Kristalle, Fp. 75–76°
12	Benzol	10	—	—

Die aus der *Fraktion* 11 gewonnenen Kristalle erwiesen sich, der Mischprobe nach, als identisch mit Pimanthren.

Die qualitative optische Untersuchung der Substanzen *A* und A_1 erfolgte unter Verwendung eines Polarisationsmikroskops. Beide Substanzen, erwiesen sich als optisch aktiv und rechtsdrehend.

Wir danken Frau Ing. E. Knížáková und Frl. B. Macounová (Laboratorium für heterocykl. Verbindungen der Tschechoslow. Akad. d. Wissenschaften) für die Ausführung der Analysen, Herrn Dr. M. Horák (Chemisches Institut der Tschechoslow. Akad. d. Wissenschaften) für die Aufnahme der Spektren, und Herrn Ing. J. Bauer (Mineral. Institut der Chem.-technol. Hochschule Prag) für seine Hilfe bei den optischen Untersuchungen.

VOL. 7 1959

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SYNTHESE VON DERIVATEN DER CINCHONA-ALKALOIDE—XXXII[1]

SYNTHESE VON DIHYDROCORYNANTHEAN UND 3-EPIDIHYDROCORYNANTHEAN AUS CINCHONIN*

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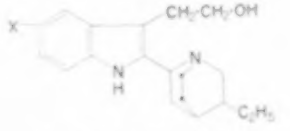
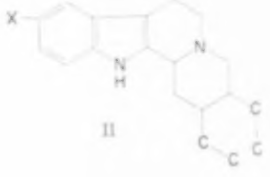
(*Received* 5 *May* 1959)

Abstract—Starting from cinchonine, 3-epidihydrocorynantheane was synthesized through 2'-oxohexahydrocinchonine. Quinine was transformed into 10-methoxydihydrocorynantheane by the same reaction steps. In both cases, it was found that Oppenauer oxidation of the secondary hydroxyl group at quinine-numbering C-9 was accompanied with no configurational change at the neighboring C-atom, which originated from C-8 in quinuclidine moiety. 3-Epidihydrocorynantheane was converted to dihydrocorynantheane by oxidation with mercuric acetate and then sodium borohydride reduction.

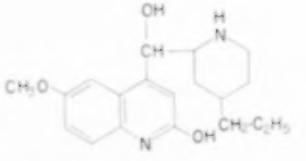
DIESE Arbeit behandelt Versuche, die Cinchona-Alkaloide in die der Corynantheinbzw. Yohimbin-Reihe zu überführen. Diese Umwandlung, die biogenetisch sehr interessant ist,[2] ist denkbar, weil, wei wir schon gezeigt haben, Dihydrocinchonamin sowie eine isomere Verbindung von seinem 5'-Methoxyderivat (Ia, Ib) aus Cinchonin bzw. Chinin ableitbar ist.[3,4] Wenn dabei ein tertiärer Chinuclidin-Stickstoff vorher in den sekundären überführbar wäre, dann könnte man durch Verknüpfung des letzteren mit der Indol-Seitenkette ein Tetrahydro-β-carbolin-Derivat (II) erhalten, welches das Grundskelett des Corynantheins enthält. Ein Modell-Versuch mit dem



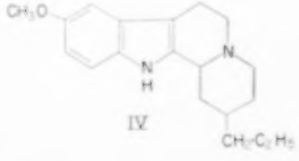
(Ia: X=H, Ib: X=OCH_3)



II



III



IV

* Als kurze Mitteilung beim *Chem. Pharm. Bull.* eingereicht.

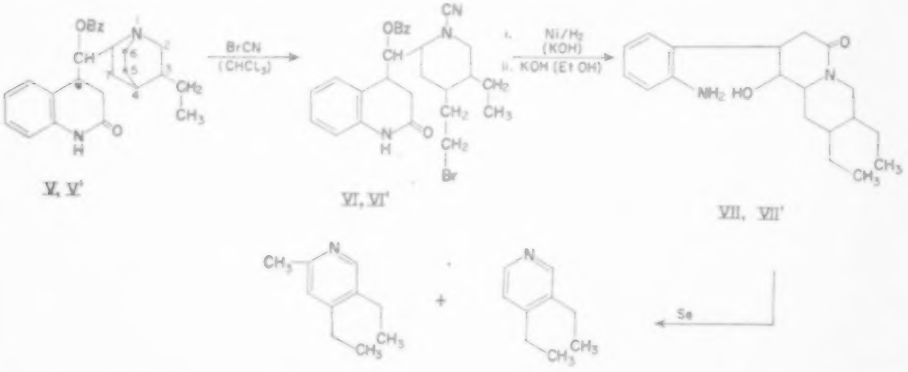
[1] XXXI. Mitteilung: E. Ochiai u. M. Ishikawa: *Chem. Pharm. Bull.* **7**, 559 (1959).
[2] Vgl. dazu: R. Goutarel, M.-M. Janot, V. Prelog u. W. Taylor, *Helv. Chim. Acta* **33**, 150 (1950); R. B. Woodward, *Angew. Chem.* **68**, 13 (1956).
[3] E. Ochiai u. M. Ishikawa, *Chem. Pharm. Bull.* **6**, 208 (1958).
[4] M. Ishikawa, *Chem. Pharm. Bull.* **6**, 71 (1958).

VOL. 7 1959

2′-Hydroxydihydronichin (III),[5] einem aus Chinin ableitbaren Sekundäramin, ergab eine Verbindung (IV), die einem Tetrahydro-β-carbolinring enthält.[6]

Ferner konnte man durch Einwirkung von Bromcyan den Chinuclidin-Teild es 2′-Oxohexahydrochinins an der Bindung zwischen dem Stickstoff und dem Kohlenstoff C-6 spalten und das entstandene Bromcyanid in eine Verbindung überführen, die höchstwahrscheinlich dem 10-Methoxydihydrocorynanthean (IX) entspricht.[1,7] Um ihre Konfiguration und damit die sterischen Beziehungen zwischen den Alkaloiden der Chinin-Reihe und denjenigen der Corynanthein- bzw. Yohimbin-Reihe klarzustellen, haben wir nun einen analogen Versuch mit dem Cinchonin durchgeführt.

Cinchonin wurde nämlich in die beiden Isomeren, Normal- und Allo-2′-oxohexahydrocinchonin,[3] überführt, und zuerst wurde die Bromcyan-Spaltung des 9-Benzoylderivates der beiden letzteren (V, V′) untersucht. 2′-Oxo-9-benzoylhexahydrocinchonin (V) (Prismen, Schmp. 225–227°) ergab dabei ein nadelförmiges Bromcyanid (VI) vom Schmp. 185–187° in einer Ausbeute von 85%, in dessen I.R.-Spektrum (in Nujol) eine Nitril-Bande bei 2215 cm^{-1} nachgewiesen wurde. VI wurde mit Raney-Nickel in Gegenwart von 1,1 mol. Kaliumhydroxyd katalytisch reduziert, und das Produkt ohne Reinigung durch Erhitzen mit 10-proz. äthanolischer Kalilauge verseift. Hiermit konnte man eine schuppenförmig kristallisierende Substanz $C_{19}H_{28}O_2N_2$ (VII) vom Schmp. 190–191° in einer Ausbeute von 44% erhalten. VII zeigte eine positive Diazoreaktion (prim. arom. Amin) und in seinem I.R.-Spektrum (in Nujol) ist eine Laktam-Bande bei 1600 cm^{-1} vorhanden. Die Selen-Dehydrierung von VII ergab 3,4-Diäthyl- und 2-Methyl-4,5-diäthylpyridin,[1,7] die durch direkten Vergleich der Pikrate identifiziert wurden. Die Konstitution von VI sowie von VII wurde damit, auch unter Berücksichtigung des Verhaltens von 2′-Hydroxydihydronichin bei der Druckhydrierung mit Raney-Nickel,[6] sicher gestellt.



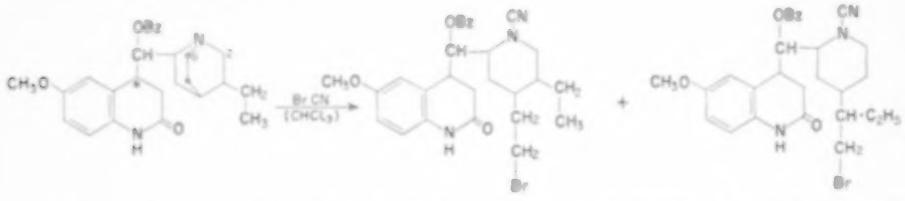
V, V′ VI, VI′ VII, VII′

Allo-2′-oxo-9-benzoylhexahydrocinchonin (V′) (Nadeln, Schmp. 253–255°) ergab analog mit Bromcyan ein nadelförmiges Bromcyanid (VI′) vom Schmp. 207–208,5° in einer Ausbeute von 94% der Theorie. In seinem I.R.-Spektrum (in Nujol) wurde das Vorliegen einer Nitril-Bande bei 2223 cm^{-1} bestätigt. VI′ wurde analog mit Raney-Nickel in Gegenwart von 1-mol. Kaliumhydroxyd katalytisch reduziert und

[5] Y. Kobayashi, *Chem. Pharm. Bull.* **6**, 273 (1958).
[6] Y. Kobayashi, *Chem. Pharm. Bull.* **6**, 732 (1958).
[7] E. Ochiai u. M. Ishikawa, *Chem. Pharm. Bull.* **7**, 256 (1959).

eine sirupöse Base (VII') erhalten, welche bei der Selen-Dehydrierung 3,4-Diäthyl- und 2-Methyl-4,5-diäthylpyridin ergab. Die Konstitution von VI' wurde somit entsprechend den angegebenen Formeln festgestellt.

Hieraus folgt, dass die Bromcyan-Spaltung von V und V' nur an der Bindung zwischen dem Chinuclidin-Stickstoff und dem Kohlenstoff C-6 mit guter Ausbeute erfolgt. Das ist sehr merkwürdig, weil bei ganz analoger Reaktion zwischen Bromcyan und den beiden isomeren 2'-Oxo-9-benzoylhexahydrochininen die Spaltung nach beiden Richtungen an der Bindung zwischen dem Stickstoff und dem Kohlenstoff C-6 sowie C-2 erfolgte.[1,7]



VII wurde ferner in einer Tetrahydrofuran-Lösung mit Lithiumaluminiumhydrid reduziert, und die entstandene Base, die nicht kristallisierte, wurde sofort der Oppenauer-Oxydation nach Ishikawa[8] mit Lithium-tert.-butoxyd und Benzophenon unterworfen. Hierdurch konnte man eine flüssige Base vom Sdp. 180–190°/10^{-3} mm

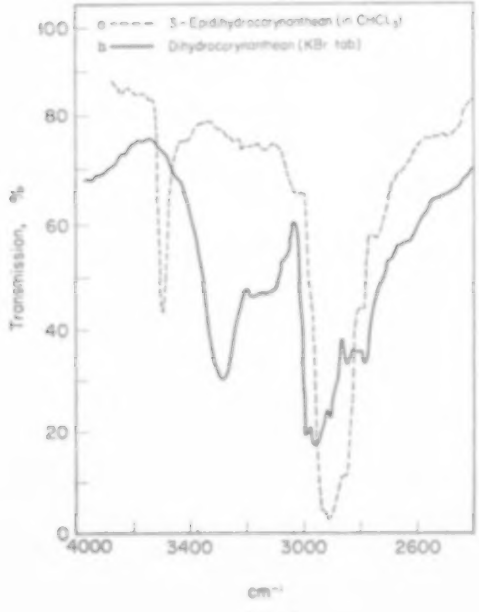
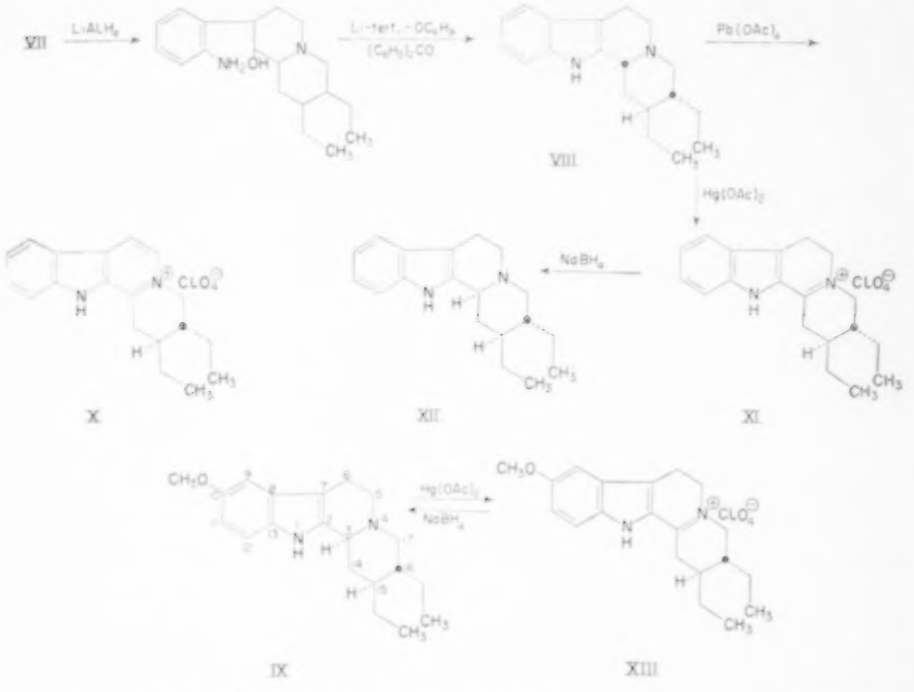


Abb. 1.

(VIII) erhalten, die als Pikrat $C_{19}H_{26}N_2 \cdot C_6H_3O_7N_3$ vom Schmp. 207–208° charakterisiert wurde. Das U.V.-Spektrum der freien Base (λ_{max}^{EtOH} : 279 mμ bei log ε: 3,83) stimmte mit demjenigen eines Indolderivates überein. In ihrem I.R.-Spektrum ist

[8] M. Ishikawa, *Chem. Pharm. Bull.* **6**, 67 (1958).

zwar eine NH-Bande bei 3500 cm^{-1} vorhanden; man konnte jedoch keine deutliche Bande eines trans-Chinolizidin-Ringes, wie beim entsprechenden Derivat (IX) aus Chinin, sondern nur eine Schulter bei 2795 cm^{-1} bemerken (Abb. 1a). (VIII) stellt also eine stereoisomere Verbindung von Dihydrocorynanthean dar, dessen Wasserstoff am C-3 höchstwahrscheinlich eine β-Konfiguration besitzt.[9] Ferner ergab VIII bei der Oxydation mit Bleitetraacetat nach Prelog und Mitarb. ein Perchlorat (schwachgelbe Würfel vom Schmp. 209–210°), welches mit dem Perchlorat von Tetradehydrodihydrocorynanthean[10] (X) gut übereinstimmte.



Ferner wurde beobachtet, dass VIII im Vergleich zu IX schwer dehydrierbar ist. Bei der Einwirkung von Merkuriacetat bei Wasserbadtemperatur zeigte IX eine ziemlich rasche Abscheidung von Merkuroacetat, während bei VIII selbst nach 2 stündigem Erhitzen fast keine Abscheidung beobachtet wurde. Dieser Unterschied bei der Dehydrierung[11,12] ist im Einklang mit der Vermutung, dass der Wasserstoff am C-3 in VIII die β- und in IX die α-Konfiguration besitzt.[13] Beim Erhitzen mit Merkuriacetat im Rohr auf 120° ergab VIII jedoch ein Didehydroderivat XI, welches als nadelförmiges Perchlorat vom Zers. Pkt. 257–259° charakterisiert wurde. In seinem I.R.-Spektrum (in KBr) sind 2 Banden bei 1640 und 1560 cm^{-1} vorhanden, welche einer konjugierten C=N-Bindung zuzuschreiben sind. Das letztere ergab bei der

[9] E. Wenkert u. D. K. Roychaudhuri, *J. Amer. Chem. Soc.* **78**, 6417 (1956).
[10] M. -M. Janot, R. Goutarel, A. Le Hir, G. Tsatsas u. V. Prelog, *Helv. Chim. Acta* **38**, 1073 (1955).
[11] N. J. Leonard, A. S. Hay, R. W. Fulmex u. V. W. Gash, *J. Amer. Chem. Soc.* **77**, 439 (1955).
[12] E. Wenkert u. D. K. Roychaudhuri, **80**, 1613 (1958).
[13] Ein Modell-Versuch zeigt, dass die Bildung des Chinolizidinrings bei der β-Konfiguration des Wasserstoffs am C-3 und mit der äquatorialen Lage beider trans-Äthylgruppen nur mit der cis-Form erreichbar ist.

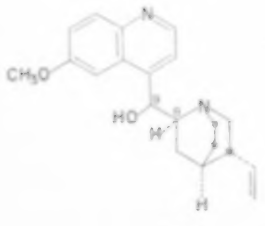
Reduktion mit Natriumborhydrid eine nadelförmige Substanz XII vom Schmp. 185,5–186°, $C_{19}H_{26}N_2$, deren Konstanten, wie aus Tabelle I hervorgeht, denen von Prelog[14] für Dihydrocorynanthean sehr ähnlich sind. Eine Mischprobe mit dem authentischen Präparat[15] (Schmp. 185–186°) zeigte keine Depression des Schmelzpunktes. Die I.R. Spektren beider Präparate (in KBr), die völlig übereinstimmten, zeigten bei 2780 und 2840 cm^{-1} die deutlichen Banden, die für die α-Konfiguration des C-3-Wasserstoffs charakteristisch sind (Abb. 1b).[9] Hierdurch wurde festgestellt, dass (XII) mit dem Dihydrocorynanthean identisch und gleichzeitig (VIII) das 3-Epidihydrocorynanthean ist.

TABELLE I

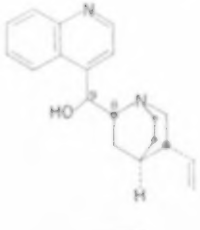
	Dihydrocorynanthean	
	nach Prelog *et al.*	(XII)
Schmp.	188,5°	185,5–186°
$(\alpha)_D$ (in CH_3OH)	−33°	−38°

Zur Kontrolle wurde IX mit Merkuriacetat in analoger Weise dehydriert und das entstandene Didehydroderivat als Perchlorat vom Zers. Pkt. 256–258° (XIII) isoliert, dessen Konstitution aus dem Vorliegen von konjugierten C=N-Banden in seinem I.R.-Spektrum (in KBr) bei 1645 und 1555 cm^{-1} bestätigt wurde. XIII ergab bei der Reduktion mit Natriumborhydrid Nadeln vom Schmp. 153–154°, die mit IX identifiziert wurden. Hiermit wurde die α-Konfiguration des Wasserstoffs am C-3 bestätigt, weil bei dieser Reduktion der Wasserstoff immer zu einer α-Konfiguration am C-3 addiert.[12,16,17] IX stellt also wirklich das 10-Methoxydihydrocorynanthean dar.

In Hinblick auf die Tatsachen, dass die Konfigurationen von Cinchona-Alkaloiden schon von Prelog und seiner Forschungsgruppe festgelegt worden sind,[18] und dass ferner die sterische Beziehung zwischen dem Corynanthein und dem Yohimbin u. dgl. auch aufgeklärt worden ist,[19] wurde mit dieser Synthese eine enge sterische und



XIV



XV

[14] M. -M. Janot, R. Goutarel u. V. Prelog, *Helv. Chim. Acta* **34**, 1207 (1951).
[15] Herrn Prof. V. Prelog in Zürich danken wir verbindlichst für die Überlassung des wertvollen Präparates Dihydrocorynanthean.
[16] E. E. Van Tamelen, P. E. Aldrich u. T. J. Katz, *Chem. & Ind.* 793 (1956).
[17] F. Weisenborn u. P. Diassi, *J. Amer. Chem. Soc.* **78**, 2022 (1956).
[18] V. Prelog u. E. Zalan, *Helv. Chim. Acta* **27**, 535, 545 (1944); V. Prelog u. O. Häfliger, *Helv. Chim. Acta* **33**, 2021 (1950).
[19] W. Klyne; *Chem. & Ind.* 1032 (1953); E. E. Van Tamelen u. M. Shamma, *J. Amer. Chem. Soc.* **76**, 950 (1954); R. E. Woodson, H. W. Youngken, E. Schlittler u. J. Schneider, *Rauwolfia* 81 (1957).

biogenetische Beziehung zwischen den Cinchona-Alkaloiden und diesen Indol-Alkaloiden enthüllt. Gleichzeitig zu betonen ist noch die Tatsache, dass bei der oben erwähnten Oppenauer-Oxydation die Konfiguration von Chinin (XIV) bzw. Cinchonin (XV) am C-8 erhalten bleibt.

BESCHREIBUNG DER VERSUCHE*

2'-Oxo-9-benzoylhexahydrocinchonin (V)

2'-Oxohexahydrocinchonin wurde in einer Lösung von Chloroform mit Benzoylchlorid in Gegenwart von 10-proz. NaOH behandelt. Prismen vom Schmp. 225–227° aus Chloroform–Methanol.

$C_{26}H_{30}O_2N_2$ Ber. C 74,61 H 7,23% Gef. C 74,21 H 7,28%

Bromcyan-Abbau von 2'-Oxo-9-benzoylhexahydrocinchonin (V)

Bromcyan-Spaltung: 12,5 g (V) wurden in 110 cm³ Chloroform gelöst. Hierauf wurde eine Lösung von 3,3 g Bromcyan (1,03 Moläquiv.) in 10 cm³ Chloroform zugesetzt und auf dem Wasserbad unter Rückfluss 1,5 Stunden lang erhitzt. Die fast farblose Reaktionslösung wurde eingedampft und der kristallinische Rückstand aus Methanol umkristallisiert. 13,4 g, Nadeln, vom Schmp. 185–187° (VI).

$C_{27}H_{29}O_3N_2Br$ Ber. C 63,02 H 5,73 N 8,02%
Gef. C 62,90 H 4,90 N 7,55%

Die methanolische Mutterlauge ergab 2,45 g schwachgelbe sirupöse Substanz, die bei der chromatographischen Reinigung durch eine Al_2O_3-Säule noch 800 mg von (VI) ergaben.

Überführung des Bromcyanids (VI) *in die Verbindung* (VII)

5,2 g (VI) wurden in 70 cm³ einer Lösung von Methanol-Dioxan (6 : 1) gelöst, 600 mg (1,1 Moläquiv.) Kaliumhydroxyd zugesetzt und mit ca. 4 g Raney-Nickel unter Wasserstoff-Atmosphäre geschüttelt. Die Wasserstoff-Aufnahme: ca. 360 cm³. Die vom Katalysator abfiltrierte Reaktionslösung wurde eingedampft und der sirupöse Rückstand mit 40 cm³ 10 proz. äthanolischer Kali-Lösung auf dem Wasserbad unter Rückfluss 8 Stunden lang erhitzt. Die Reaktionslösung wurde bis etwa zur Hälfte eingedampft, mit 20 cm³ Wasser versetzt, stehengelassen, und die hierbei ausgeschiedenen Kristalle wurden abgesaugt. Die Mutterlauge wurde mit Kohlendioxyd gesättigt, 1 Stunde lang auf dem Wasserbad erhitzt und nach Zusatz von etwas Wasser mit Chloroform ausgezogen. Die Chloroform-Lösung wurde über Natriumsulfat getrocknet, eingedampft, und der Rückstand wurde aus Methanol–Wasser umkristallisiert. Die so erhaltenen Kristalle wurden mit den oben erhaltenen Kristallen vereinigt und aus Methanol–Wasser umkristallisiert. 1,4 g schuppenförmige Kristalle vom Smp. 190–191° (VII).

$C_{19}H_{23}O_2N_2$ Ber. C 72,11 H 8,92 N 8,85%
Gef. C 71,53 H 8,68 N 8,80%

I.R. : ν_{max}^{Nujol} cm^{-1}: 3370, 3300, 3250 (NH_2 und OH); 1600 (CON).

Selen-Dehydrierung von VII: 400 mg (VII) wurden mit 500 mg pulverisiertem Selen innig gemischt und im Stickstoff-Strom 3 Stunden lang auf 320–340° erhitzt. Nach dem Erkalten wurde die Reaktionsmischung mit Äther und dann mit Benzol durch Digerieren extrahiert, und die beiden vereinigten Auszüge wurden mit 10 proz. Salzsäure ausgezogen. Die Salzsäure-Lösung wurde mit Natronlauge stark alkalisch gemacht und mit Äther umgeschüttelt. Die ätherische Lösung wurde nach dem Trocknen über Kaliumcarbonat eingedampft, der Rückstand durch Erhitzen im Ölbad auf 205–210° destilliert und das Destillat über das Pikrat gereinigt. 85 mg rohes Pikrat vom Smp. 125–144°. Die aus diesem Pikrat befreite ölige Base wurde in einer Lösung von Petroläther-Äther (30 : 1) durch eine Al_2O_3-Säule chromatographisch gereinigt. Die erneut dargestellten Pikrate wurden durch Umkristallisieren aus Methanol gereinigt. Die ersten Eluate ergaben 18 mg Nadeln vom Schmp. 165–166,5°, die durch eine Mischprobe mit dem Pikrat von 2-Methyl-4,5-diäthylpyridin identifiziert wurden. Die folgenden Fraktionen ergaben 20 mg Nadeln vom Schmp. 138–139°, die durch eine Mischprobe mit dem Pikrat von 3,4-Diäthylpyridin identifiziert wurden.

* Schmp. nicht korrigiert.

Allo-2′-oxo-9-benzoylhexahydrocinchonin (V′)

Allo-2-oxohexahydrocinchonin wurde analog dem 2′-Oxohexahydrocinchonin benzoyliert. Nadeln aus Chloroform, Schmp. 253–255°.

$C_{26}H_{28}O_3N_2$ Ber. C 74,61 H 7,23% Gef. C 74,30 H 7,85%

Bromcyan-Abbau des Allo-2′-oxo-9-benzoylhexahydrocinchonins (V′)

Bromcyan-Spaltung: Der Lösung von 9,6 g (V′) in 90 cm³ Chloroform wurde eine Lösung von 2,5 g (1,02 Moläquiv.) Bromcyan in 10 cm³ Chloroform zugefügt und analog der Spaltung von (V) zur Einwirkung gebracht. Die Reaktionslösung wurde eingedampft und der Rückstand mit Methanol behandelt. Das hierbei ausgeschiedene kristallinische Produkt wurde abgesaugt und aus Methanol umkristallisiert. 11,2 g Nadeln vom Schmp. 207–208,5° (VI′).

$C_{27}H_{30}O_3N_3Br$ Ber. C 63,02 H 5,73 N 8,02%
Gef. C 62,06 H 5,05 N 7,76%

Überführung vom Bromcyanid (VI′) *in die Verbindung* (VII′)

Die Lösung von 2,1 g (VI′) in 40 cm³ Methanol-Dioxan (1 : 1) wurde mit 220 mg Kaliumhydroxyd (1 Moläquiv.) und ca. 2 g Raney-Nickel versetzt und mit Wasserstoff geschüttelt. Die Wasserstoff-Aufnahme betrug ca. 160 cm³. Die vom Katalysator abfiltrierte Reaktionslösung wurde analog der Reduktion von (VI) aufgearbeitet. 1,6 g sirupöse Basen (VII′) wurden erhalten, die analog mit Selen dehydriert und aufgearbeitet wurden. Hierbei wurden 2 basischen Fraktionen erhalten, die als Pikrat vom Schmp. 138–139° bzw. Schmp. 165–166,5° mit 3,4-Diäthyl- bzw. 2-Methyl-4,5-diäthyl-pyridin identifiziert wurden.

Überführung von VII *in* 3-*Epidihydrocorynanthean* (VIII)

1,1 g (VII) wurden in einem Soxhlet-Apparat mit einer Lösung von 320 mg Lithiumaluminium-hydrid in 30 cm³ Tetrahydrofuran extrahiert. Nachdem alle Kristalle in Lösung gegangen waren, wurde die Lösung noch 2,5 Stunden lang unter Rückfluss erhitzt, mit wasserhaltigem Äther das überschüssige Lithiumaluminiumhydrid zersetzt und mit 10 proz. Natronlauge geschüttelt. Die ätherische Lösung wurde nach dem Trocknen über Kaliumcarbonat eingedampft, der Rückstand in einer Lösung von wenig Methanol in Chloroform durch eine Al_2O_3-Säule chromatographisch gereinigt, wobei 950 mg sirupöse Base erhalten wurde, die nicht kristallisierten. Die ganze Menge wurde mit 1 g Lithium-tert.-butoxyd, 7 g Benzophenon und 11 cm³ Benzol versetzt und in einem mit Stickstoff gefüllten Rohr 50 Stunden lang auf 110–115° erhitzt. Die Reaktionsmischung wurde nach Zusatz von Äther mit Wasser gewaschen, eingedampft, der Rückstand mit 30 cm³ Petroläther und 10 cm³ chlorwasserstoff-haltigem Äther umgeschüttelt und stehengelassen. Das hierbei ausgeschiedene sirupöse Hydrochlorid wurde nach dem Abdekantieren des Lösungsmittels in Chloroform aufgenommen, die Lösung mit verd. Ammoniak gewaschen und nach dem Trocknen über Natriumsulfat eingedampft. Der Rückstand wurde in einer Lösung von Äther durch eine Al_2O_3-Säule filtriert, das Filtrat eingedampft und der sirupöse Rückstand als Pikrat durch Umkristallisieren aus Methanol gereinigt. Blätterförmiges Pikrat vom Schmp. 207–208° (670 mg).

$C_{19}H_{26}N_2 \cdot C_6H_3O_7N_3$ Ber. C 58,70 H 5,71 N 13,69%
Gef. C 59,06 H 5,76 N 13,57%

Die vom Pikrat befreite Base (VIII) ist ölig, Sdp. 180–190°/10^{-3} mm.

Dehydrieren von VIII *mit Bleitetraacetat*

250 mg (VIII) wurden in 3 cm³ Essigsäure gelöst, auf 60° erwärmt und mit 800 mg Bleitetraacetat portionsweise unter Umschütteln versetzt. Die gelbrot gefärbte Reaktionslösung wurde auf 100 cm³ mit Wasser verdünnt, mit Natriumcarbonat schwach alkalisch gemacht und mit Chloroform ausgezogen. Die Chloroform-Lösung wurde nach dem Trocknen über Natriumsulfat durch eine kurze Al_2O_3-Säule filtriert, die adsorbierte quartäre Base mit Methanol-Chloroform eluiert und das

Eluat als Perchlorat unter einmaliger Behandlung mit aktiver Kohle aus Methanol-Wasser umkristallisiert. 45 mg schwachgelbe Würfel (X) vom Schmp. 209–210°.

$C_{19}H_{22}N_2 \cdot ClO_4$ Ber. C 60,16 H 6,07 N 7,39%
Gef. C 60,41 H 5,93 N 6,95%

U.V.: λ_{max}^{EtOH} mμ (log ε): 251 (4,34), 307 (4,17), 354 (4,21).
λ_{min}^{EtOH} mμ (log ε): 225 (4,13), 279 (3,59), 319 (3,78).

Oxydation von VIII *mit Merkuriacetat*

360 mg (VIII) wurden in 30 cm³ 5 proz. Essigsäure gelöst, mit 1,42 g Merkuriacetat (4 Moläquiv.) versetzt und in einem mit Stickstoff gefüllten Rohr 3 Stunden lang auf 120° erhitzt. Nach dem Erkalten wurde das ausgeschiedene Merkuroacetat abfiltriert, das Filtrat mit Schwefelwasserstoff gesättigt, unter Zusatz von einer geringen Menge konz. Salzsäure auf dem Wasserbad erhitzt und das koagulierte Merkurisulfid abfiltriert. Das schwachgelbe Filtrat ergab beim Zusatz von Natriumperchlorat-Lösung einen kristallinen Niederschlag, welcher abgesaugt und aus Methanol umkristallisiert wurde. 240 mg schwachgelbe Nadeln vom Zers. Pkt. 257–259° (XI).

$C_{19}H_{23}N_2 \cdot ClO_4$ Ber. C 59,91 H 6,62 N 7,36%
Gef. C 60,33 H 5,76 N 7,29%

U.V.: λ_{max}^{EtOH} 354 mμ (log ε: 4,24). λ_{min}^{EtOH} 275 mμ (log ε: 3,26).

Reduktion von XI *mit Natriumborhydrid*

Der Lösung von 500 mg Natriumborhydrid (25 Moläquiv.) in 15 cm³ Methanol wurden 210 mg (XI) zugesetzt und 3 Stunden lang auf dem Wasserbad unter Rückfluss erhitzt. Die Reaktionslösung wurde nach Zusatz einer geringen Menge Aceton im Vakuum eingedampft, der Rückstand mit etwas Wasser versetzt und in Chloroform aufgenommen. Die Chloroform-Lösung wurde nach dem Trocknen über Natriumsulfat eingedampft, der kristalline Rückstand in Äther aufgenommen, die Äther-Lösung durch eine kurze Al_2O_3-Säule filtriert und das Filtrat eingedampft. Der Rückstand ergab beim Umkristallisieren aus Äther–Petroläther oder aus Methanol 120 mg Nadeln vom Schmp. 185,5–186° (XII). $(\alpha)_D^{13}$: −38° (c = 0,96, Methanol. l = 1 dm).

$C_{19}H_{26}N_2$ Ber. C 80,80 H 9,27 N 9,93%
Gef. C 81,27 H 8,95 N 9,90%

Eine Mischprobe mit dem Dihydrocorynanthean vom Schmp. 185–186°[15] schmolz bei 185,5–186°.

Oxydation von 10-*Methoxydihydrocorynanthean* (IX) *mit Merkuriacetat*

100 mg (IX) wurden in 10 cm³ 5 proz. Essigsäure gelöst und 370 mg (4 Moläquiv.) Merkuriacetat zugesetzt. 50 Minuten lang wurde auf dem Wasserbad erhitzt, wobei die Abscheidung von Merkuroacetat schon nach 2–3 Minuten bemerkbar war. Nach dem Erkalten wurde das Merkuroacetat abfiltriert und das Filtrat analog der Oxydation von (VIII) mit Merkuriacetat aufgearbeitet. 72 mg schwachgelbes Perchlorat vom Zers. Pkt. 256–258° (XIII) wurden erhalten.

$C_{20}H_{27}ON_2 \cdot ClO_4$ Ber. C 58,39 H 6,62 N 6,82%
Gef. C 58,50 H 6,09 N 6,62%

U.V.: λ_{max}^{EtOH}: 367 mμ (log ε: 4,38); λ_{min}^{EtOH}: 285 mμ (log ε: 2,86).

Reduktion von XIII *mit Natriumborhydrid*

(XIII) wurde ganz analog wie beim (XI) mit Natriumborhydrid reduziert und Nadeln vom Schmp. 153–154° (aus Äther-Petroläther) erhalten. Eine Mischprobe mit (IX) schmolz bei 153–154°.

VOL. 7 1959

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TERPENOIDS—VI

A NOVEL UNAMBIGUOUS SYNTHESIS OF DL-AR-TURMERONE[1]

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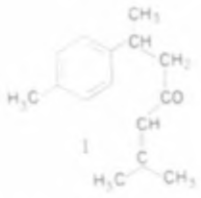
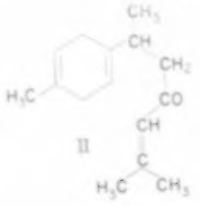
(*Received* 27 *February* 1959)

Abstract—A new synthesis of DL-ar-turmerone starting from DL-curcumone is described.

The aromatic ketone DL-ar-turmerone (I) occurs with turmerone (II) a monocyclic sesquiterpene ketone, as chief component of the essential oil from the rhizomes of *Curcuma longa* Linn.

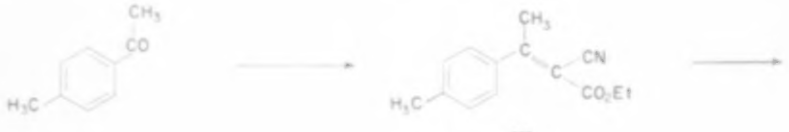


I

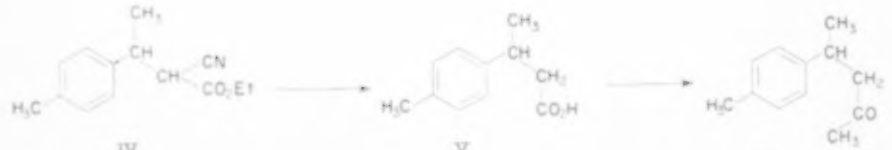


II

THE structure of I was determined by Rupe and co-workers,[3,4] and confirmed by a number of syntheses.[3,5,6] We now record a new synthesis of DL-ar-turmerone by a direct and simpler sequence of reactions, involving the intermediate formation of the 3-hydroxy-1-keto-(1-dioxolane)-alkane system which serves as a precursor of the final $\alpha\beta$-unsaturated ketone.[7,8] The starting material, curcumone (VI), was obtained as follows:



III



IV V VI

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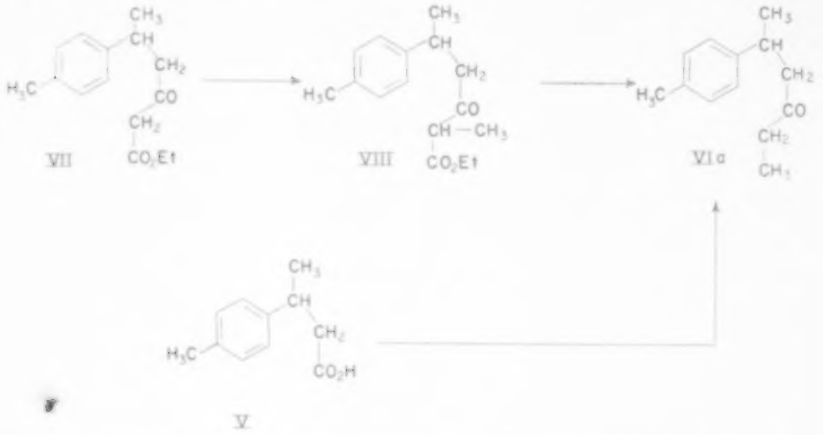
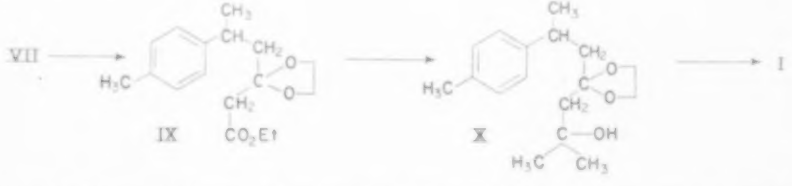
VOL. 7 1959

Ethyl β-methyl-β-(p-tolyl)-α-cyanoacrylate (III) was obtained by Cope–Knoevenagel condensation of p-methyl acetophenone and ethyl cyanoacetate.[9,10] The ester (III) was reduced catalytically in almost quantitative yield to ethyl α-cyano-β-methyl-β-(p-tolyl)-propionate (IV) which on hydrolysis gave β-(p-tolyl)-butyric acid (V). The acid chloride from V was treated with cadmium dimethyl reagent in benzene and refluxed,[11] yielding β-methyl-β-(p-tolyl)-ethylmethyl ketone (Curcumone VI), which was characterized as its semicarbazone derivative.[4] A better and consistent yield (88%) (based on acid chloride) of the ketone (VI) was, however, obtained by using the method of Walker and Hauser.[12] VI was carbethoxylated with sodium hydride in large excess of diethylcarbonate[13] to ethyl β-keto-δ-methyl-δ-(p-tolyl)-valerate (VII). The position of the ethoxycarbonyl group in VII is assumed by analogy,[14] as well as mixed melting point of the 2:4-dinitrophenylhydrazone derivates of 5-methyl-5-(p-tolyl)-pentane-3-one (VIa) derived in two ways as indicated in the following scheme:



VII was ketalized with ethylene glycol to obtain ethyl β-keto-(β-dioxolane)-δ-methyl-δ-(p-tolyl)-valerate (IX):



IX reacted with methyl magnesium iodide giving the carbinol (X). The ketal-alcohol (X) was then subjected to acid hydrolysis and subsequently distilled in the presence of trace of iodine to obtain DL-ar-turmerone (I). The unsaturated ketone gave a semicarbazone.

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EXPERIMENTAL*

Ethyl α-cyano-β-methyl-β-(p-tolyl)-acrylate (III)

(a) A mixture of *p*-methyl-acetophenone (134 g), ethyl cyanoacetate (113 g), ammonium acetate (15·5 g), acetic acid (48 g) and anhydrous benzene (300 ml) was refluxed under a Dean and Stark apparatus for 15–20 hr. The contents were cooled, water added and the organic substance extracted in ether–benzene. The vacuum distillation of the product gave 140 g (61%) of a viscous oil, b.p. 160–170°/10 mm (Found: C, 73·1; H, 6·75. $C_{14}H_{15}O_2N$ requires: C, 73·34; H, 6·59%).

(b) A mixture of *p*-methylacetophenone (67 g), ethyl cyanoacetate (113 g), ammonium acetate (6 g), acetic acid (48 g), and benzene was refluxed under a water separator until no more water came over. Ammonium acetate (2 g) was added and the contents refluxed for 3–4 hr. Refluxing was again interrupted several times till a total of 16 g of the ammonium acetate had been added. Heating was continued for several hours after the last addition of the catalyst. As in (a) 80 g (70%) of III was obtained.

Ethyl α-cyano-β-methyl-β-(p-tolyl)-propionate (IV)

(a) The alkylidene ester (III, 50 g) was reduced in alcohol (98%, 200 ml) and acetic acid (2–3 ml) with Pd-charcoal (5%, 5 g). Hydrogen gas (5400 ml) was absorbed, yielding the reduction product (45 g, 90%), b.p. 160–162°/10 mm (Found: C, 72·70; H, 7·41. $C_{14}H_{17}O_2N$ requires: C, 72·45; H, 7·30%).

(b) The hydrogenation proceeded more rapidly when Pd-strontium carbonate (10%) was employed as catalyst in ethanol.

β-Methyl-β-(p-tolyl)-propionic acid (V)

IV (100 g) was refluxed with conc HCl (600 ml) for about 50 hr. After cooling the crude material (58 g, 76%) m.p. 87–88° was purified through its sodium salt.

The analytical sample obtained after crystallization from ethanol, m.p. 90·5°, lit.[4] m.p. 91°. (Found: C, 73·8; H, 7·68. $C_{11}H_{14}O_2$ requires: C, 74·13; H, 7·92%).

β-Methyl-β-(p-tolyl)-propionyl chloride

The acid (V, 50 g), diluted with anhydrous benzene (100 ml), and thionyl chloride (70 g) were heated (water bath) for about 2 hr. After removal of benzene and excess thionyl chloride, the acid chloride was distilled at 120°/5 mm yield, 50 g (90·6%).

β-Methyl-β-(p-tolyl)-ethylmethyl ketone (VI)

(a) To the well-cooled Grignard reagent (prepared from 13·2 g Mg, 78 g methyl iodide and 300 ml dry ether) was added, with stirring, anhydrous cadmium chloride (46·5 g), and the mixture refluxed for 3–4 hr. Ether was replaced by anhydrous benzene (400 ml). The acid chloride (44 g) was added slowly refluxing the benzene for an additional 1½ hr. The contents were decomposed with dil ice-cold H_2SO_4 and ether extracted, washed free of acid, dried. The ketone (VI) 29·5 g, 75% was obtained as a light oil, b.p. 130°/12 mm. The semicarbazone after crystallization from dil alcohol, melted at 145°, lit.[4] m.p. 146°. (Found: N, 17·5. $C_{13}H_{17}ON_3$ Calc. for N, 18·01%).

(b) Ethoxymagnesium malonate was prepared from magnesium metal (2·68 g), absolute ethanol (13 ml), anhydrous ether (50 ml) and diethyl malonate (17·6 g) according to the procedure of Walker and Hauser.[12] The acid chloride (19·7 g) was added during stirring and the contents refluxed for an additional ½ hr. After cooling, the reaction mixture was decomposed with dil H_2SO_4 and the acyl malonic ester derivative ether extracted and the solvent evaporated. The residue was refluxed with a mixture of glacial acetic acid (30 ml), water (20 ml) and conc H_2SO_4 (5 ml) for 5 hr. KOH (20%) was added till alkaline and the product extracted with ether, which on distillation yielded 15·5 g (88%) of the ketone (VI), b.p. 130°/12 mm.

The semicarbazone m.p. and mixed m.p. with the sample obtained in (a), 144–145°.

* Melting and boiling points are uncorrected. Microanalyses by Drs. Weiler and Strauss, Oxford.

Ethyl β-keto-δ-methyl-δ-(p-tolyl)-valerate (VII)

VI (16·3 g) was added with stirring to a refluxing mixture of sodium hydride (4·8 g), anhydrous ether (500 ml) and diethyl carbonate (23·6 g). After the addition the contents were stirred and refluxed for another 2 hr and the mixture decomposed with cold dilute acetic acid and extracted with ether. The ethereal solution was washed once with water, then with 5% sodium bicarbonate solution until free of acid, and finally with water and dried. After the removal of ether, the residual heavy oil was distilled under reduced pressure. The fraction distilling at 190–193°/10 mm was collected; yield, 9·6 g (42%).

The β-keto-ester gave a violet-red coloration with alcoholic ferric chloride solution. (Found: C, 72·20; H, 7·85. $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·12%).

Ethyl β-keto-αδ-dimethyl-δ-(p-tolyl)-valerate VIII)

VII (5 g) was added to a cooled solution of potassium metal (1 g), in dry t-butyl alcohol (50 ml) and the mixture left for 4–6 hr until the solution became strongly coloured (orange). Thereafter, it was heated on the water-bath for ½ hr and again cooled. Methyl iodide (4 g) was introduced and the mixture refluxed for 3–4 hr and the t-butyl alcohol was distilled. Water was added to dissolve potassium iodide and the organic material ether extracted. From the dried ethereal solution (4 g, 75%) of the oily methyl-keto-ester (VIII) distilling at 170–175°/4 mm was obtained. (Found: C, 72·8; H, 8·5. $C_{16}H_{22}O_3$ requires: C, 73·25; H, 8·45%).

5-*Methyl*-5-(p-*tolyl*)-*pentan*-3-*one*(*homo-curcumone*) (VIa)

(a) *The reaction of curcumic acid chloride with cadmium diethyl.* Cadmium diethyl reagent was prepared from ethyl bromide (13·1 g), magnesium turnings (3 g), anhydrous cadmium chloride (11 g) in dry ether (50 ml). Ether was replaced by benzene (75 ml) and to the refluxing mixture, with stirring, curcumic acid chloride (12 g) in anhydrous benzene (25 ml) was added during 15 min and stirring and refluxing continued for another 20 min. Homocurcumone (9 g, 77·5%) b.p. 125°/5–6 mm, was obtained as a colourless oil. (Found: C, 82·42; H, 9·63. $C_{13}H_{18}O$ requires: C, 82·06; H, 9·54%).

The 2:4-dinitrophenylhydrazone of VIa was deposited as yellow needles which after two crystallizations from ethyl acetate-methanol mixture melted at 113–114°. (Found: N, 15·7. $C_{19}H_{22}O_4N_4$ requires: N, 15·2%).

(b) *The hydrolysis of* (VIII). The keto-ester (VIII, 3 g) was refluxed with a mixture of conc H_2SO_4 (2 ml), acetic acid (8 ml) and water (5 ml) for 5–6 hr. After cooling, sufficient potassium hydroxide solution (20%) was added until alkaline. The ethereal solution of the oily product was washed free of alkali, dried and the solvent evaporated leaving the ketone (VIa) b.p. 125°/5–6 mm.

The 2:4-dinitrophenylhydrazone, m.p. 113° was undepressed on admixture with the sample of 2:4-dinitrophenylhydrazone obtained as in (a).

Ethyl (*β-keto-β-dioxolane*)-*δ-methyl-δ-*(p-*tolyl*)-*valerate* (IX)

The keto-ester (VII, 10 g), ethylene glycol (4 g), *p*-toluene-sulphonic acid (0·1 g) and anhydrous benzene (100 ml) were refluxed (oil-bath at 120°) under a constant water separator for 6 hr. After cooling, sodium ethoxide in alcohol and water was added, and the organic material extracted with ether. This yielded (9·28 g, 88%) of IX as a colourless viscous oil, b.p. 218–220°/12 mm (Found: C, 69·5; H, 8·3. $C_{17}H_{24}O_4$ requires: C, 68·83; 8·27%).

(*β-Keto-β-dioxolane*)-*δ-methyl-δ-*(p-*tolyl*)-n-*butyl-dimethyl carbinol* (X)

Grignard reagent was prepared from clean dry magnesium turnings (1·8 g), and methyl iodide (11 g) in dry ether (100 ml). To this was added the ketal-ester (IX, 10 g) dropwise under ice-cooling. The contents were allowed to stand overnight at room temp and then refluxed for an hour. After cooling, the reaction mixture was decomposed with saturated ammonium chloride solution. On subsequent working up the ketal-carbinol (X) was obtained as a colourless viscous oil yield, 7·3 g (76%), b.p. 222–225°/10 mm. (Found: C, 73·5; H, 9·0. $C_{17}H_{28}O_3$ requires: C, 73·34; H, 9·41%).

DL-ar-Turmerone (I)

The above ketal-alcohol (X, 7·3 g) was refluxed for an hour with a solution of ethanol (30 ml), water (100 ml) and four drops of conc HCl. The mixture was then cooled, diluted with water (50 ml) and extracted with ether. The dried ethereal extract was evaporated and the residue was distilled under reduced pressure with a crystal of iodine yielding 4·37 g (64%) of a light oil, b.p. 156–158°/7 mm. η_D^{21} 1·5218. (Found: C, 83·0; H, 9·48. $C_{15}H_{20}O$ requires: C, 83·28; H, 9·32%).

The semicarbazone of I crystallized from dil ethanol in colourless needles, m.p. 105–106.° Lit.[3] m.p. 108° for D-ar-turmerone semicarbazone. (Found: N, 15·1. $C_{16}H_{23}ON_3$ requires: N, 15·37).

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VOL. 7 1959

STUDIES IN RELATION TO BIOSYNTHESIS—XXI*

ROSENONOLACTONE AND GIBBERELLIC ACID

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and

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(*Received* 18 *April* 1959)

Abstract—The biosyntheses of rosenonolactone in *Trichothecium roseum* and of gibberellic acid in *Gibberella fujikuroi* have been studied by feeding experiments with $CH_3{}^{14}CO_2Na$ and (2-^{14}C)-mevalonic lactone. Preliminary accounts[1-2] of this work have been published.

IN choosing moulds for experimental studies in the biosynthesis of terpenoid compounds we took account of the ease of culturing the organisms, the simplicity of techniques for incorporating substrates and the variety of terpenoid metabolites, including some with C_5, C_{10} or related units. The field therefore seemed to offer advantages over the classical squalene–lanosterol–cholesterol system hitherto investigated in liver or in yeast. Our first experiments[4] confirmed that the geranyl-type chain in mycelianamide (I), from *Penicillium griseofulvum*, and the oxidised geranyl chain in mycophenolic acid (II), from *P. brevi-compactum* are derived from mevalonic lactone (III) (C* = ^{14}C). More recently,[5] the simple isopentenyl side-chain of auroglaucin (IV) has also been shown to come from III. Evidence was also obtained in these organisms that mevalonic acid is derived from acetic acid.

In agreement with results obtained by other workers[6] for squalene and carotenoid biosynthesis, we observed that the *w*-carbon atoms (Klyne nomenclature[7]) of the isoprene units are derived specifically from the 2-position of mevalonic lactone. With (2-^{14}C)-mevalonic lactone as substrate, the label was confined to the main chains of I and II, there being no labelling on the *w'*-carbon atom. From this it is logical to inquire whether asymmetry of labelling persists in the terminal *gem*-dimethyl groups of a terpene chain. The difference between these groups is solely stereochemical, and by analogy with the normal *trans*-double bonds found in the chain of, for example, squalene, the methyl group *trans*- to the main chain should

* Part XX: A. J. Birch, O. C. Musgrave, R. W. Richards and H. Smith, *J. Chem. Soc.* In press.

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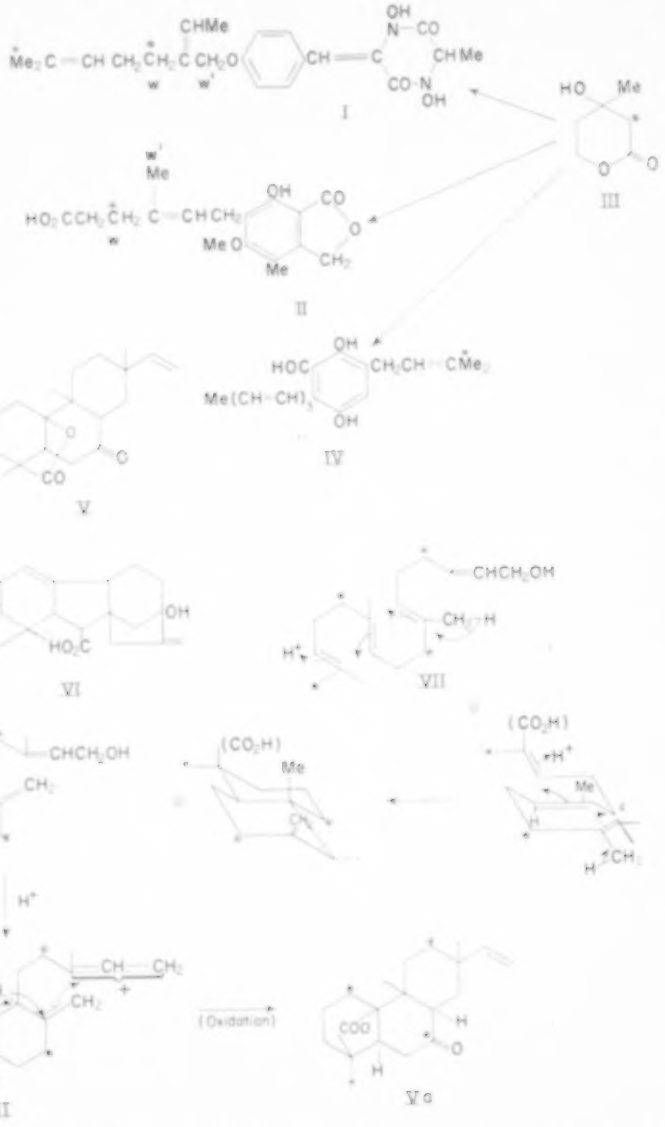
[4] A. J. Birch, R. J. English, R. A. Massy-Westropp and H. Smith, *Proc. Chem. Soc.* 233 (1957); *Idem. J. Chem. Soc.* 369 (1958).
[5] A. J. Birch, J. Schofield and H. Smith, *Chem. & Ind.* 1321 (1958).
[6] J. W. Cornforth, R. H. Cornforth, G. Popjak and I. Youhotsky-Gore, *Biochem. J.* **66**, 10P (1957); **69**, 146 (1958); B. H. Amdur, H. Rilling, and K. Bloch, *J. Amer. Chem. Soc.* **79**, 2647 (1957); G. D. Braithwaite and J. W. Goodwin, *Biochem. J.* **67**, 13P (1957).
[7] W. Klyne, *Chem. & Ind.* 725 (1954).

contain all of the label. This situation is difficult to investigate experimentally in the readily available substances methylgeraniolene (obtained by reductive fission of



mycelianamide[4]) and squalene, biosynthesized from (2-^{14}C)-mevalonic lactone, because of the difficulty of distinguishing chemically between these two methyl groups. Asymmetry of labelling would be expected to persist in enzymatically cyclized products of such a chain, provided that the reactions are concerted and do not involve "free" cations. Questions covering distribution of label and the concerted mechanism of cyclization can be settled simultaneously by examining cyclic mould metabolites in which the relevant carbon atoms are chemically distinguishable.

Two suitable substances are known: rosenonolactone, structurally probably V,[8] and gibberellic acid (VI) the structure of which has been elucidated through the notable work of Grove, and his colleagues.[9]

Biosynthetically, rosenonolactone appears to be a diterpene which has suffered migration of a methyl group from the 12- to the 13-position. A route can be formulated as in the sequence (VII) → (VIII) → (Va) in line with current ideas on terpene cyclizations.[10]† No information is available as to the exact stages when the oxidations occur.

VOL. 7 1959

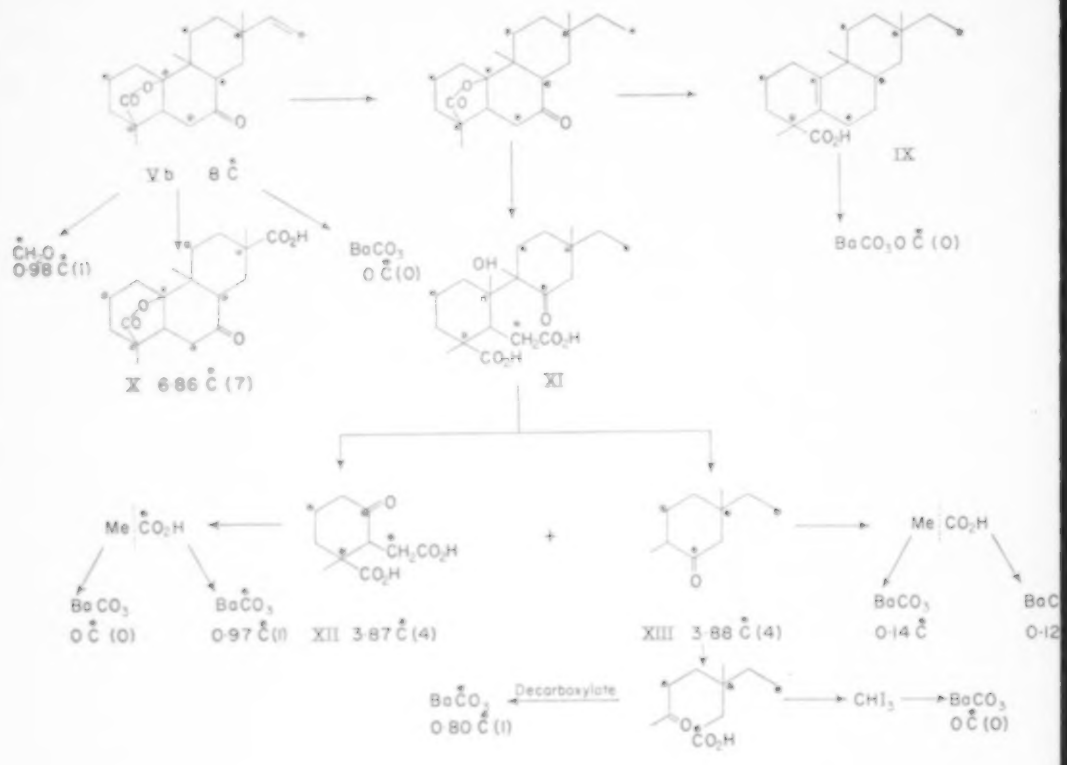
The metabolite was produced in cultures containing either $CH_3{}^{14}CO_2H$ or [2-^{14}C]-mevalonic lactone, the incorporation of radioactivity being 4 per cent in each case. The labelled material was degraded by methods chiefly developed in the earlier structure work.[8] The results are summarized in Schemes A and B on p. 244. The expected labelling patterns from $Me^{14}CO_2H$ and [2-^{14}C]-mevalonic lactone are Vb and Va respectively ($C^* = {}^{14}C$). The numbers of active carbon atoms shown for each degradation product are calculated from the radioactive assay data on the assumption that there are eight equally labelled carbon atoms in the rosenonolactone derived from $Me^{14}CO_2H$ and four when [2-^{14}C]-mevalonic lactone is the source. It will be seen that the results are in quantitative agreement with the expected distributions. Furthermore the derivation of the 1-Me group but not the 1-carbonyl group from the 2-position of mevalonic lactone confirms that the acyclic precursor must have the *gem*-dimethyl group unsymmetrically labelled and that the cyclization to the first two rings is a concerted one. Since the molar activity of ketone (XIII) is calculated on a formula $C_{10}H_{18}O$ the migration of the Me-group from the 12- to the 13-position is confirmed.

Work on gibberellic acid was pursued simultaneously. Inspection of the structure VI indicated a possible biosynthesis by a variant of the resin-acid process involving, besides oxidation, a number of additional steps for which there are biochemical or laboratory analogies. These include (a) oxidative loss of the methyl group attached to the 12-position; (b) formation of a phyllocladene-type bridged ring system from ring C and its substituents, and (c) ring contraction of ring B with extrusion of a carbon atom and formation of a cyclopentane carboxylic acid unit. Step (a) would be analogous to the loss of the angular group attached to the 14-position in the lanosterol–cholesterol conversion;[11] step (b) has a laboratory analogy in the acid-catalysed transformation of rimuene to phyllocladene[12] and, in view of the occurrence of diterpenes with oxygen substituents in the 9- or 10-positions or both (e.g. rosenonolactone, rosololactone[13] which occur together, and xanthopherol[14]) there is no difficulty in accepting the possibility that step (c) proceeds through a 9:10-dioxygenated derivative. A number of base-catalysed rearrangements for the change are available including: (i) a benzil-benzilic acid type of transformation of a 1:2-diketone leading to a 1-hydroxycyclopentane carboxylic acid; (ii) a Faworski-type rearrangement of

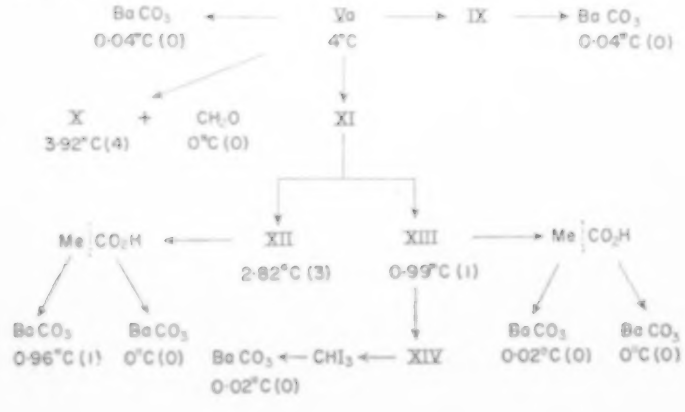
† See below for a discussion of the stereochemistry.

[8] A. Harris, A. Robertson and W. B. Whalley, *J. Chem. Soc.* 1799 (1958) and earlier papers.
[9] B. E. Cross, J. F. Grove, J. MacMillan, T. P. C. Mulholland and N. Sheppard, *Proc. Chem. Soc.* **221** (1958); T. P. C. Mulholland, *J. Chem. Soc.* 2693 (1958), and earlier papers.
[10] For a recent review see L. Ruzicka, *Perspectives in Organic Chemistry* (Edited by Todd) p. 265. Interscience, New York (1957).
[11] For a review see K. Bloch, *Vitamins and Hormones* Vol 15, p. 119. Academic Press, New York (1957).
[12] L. H. Briggs, B. F. Cain and J. K. Wilmshurst, *Chem. & Ind.* 599 (1958).
[13] A. Harris, A. Robertson and W. B. Whalley, *J. Chem. Soc.* 370 (1958).

Scheme A

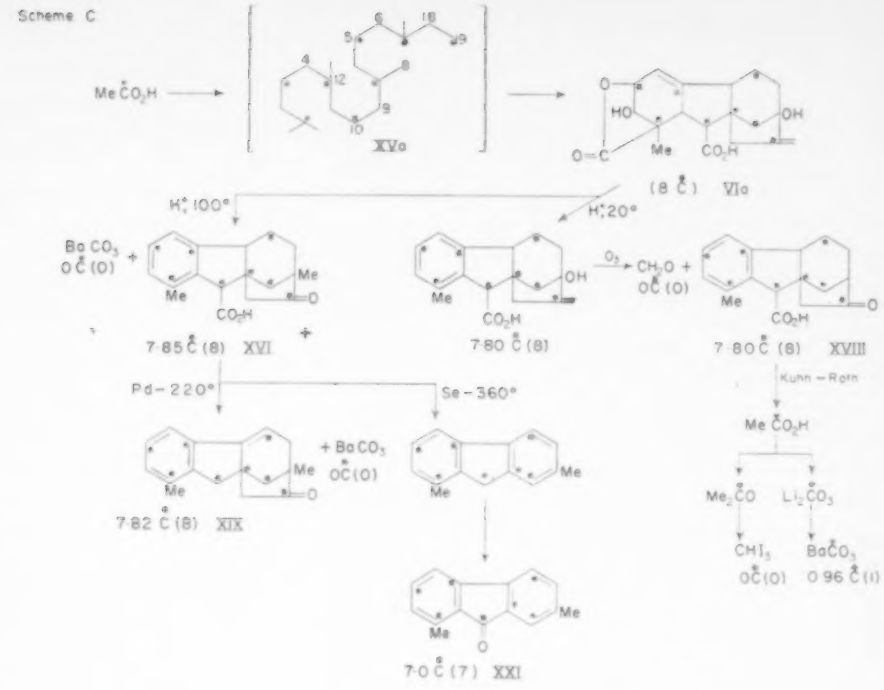


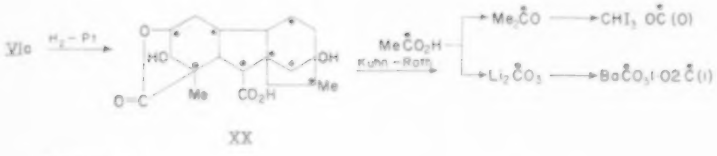
Scheme B



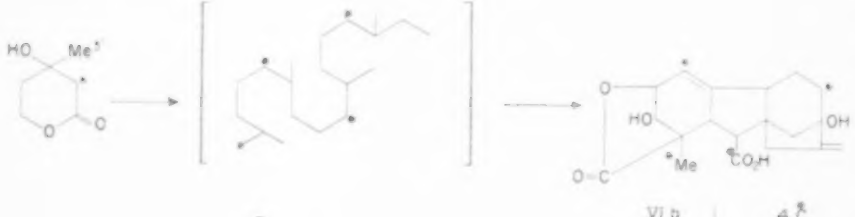
VOL. 7 1959

Scheme C





Scheme D



XVI + BaCO3
3·89 C* (4) 0·02 C* (0)

XXI
2·88 C* (3)

XIX + BaC*O3
2·92 C* (3) 1·01 C* (1)

XVII → CH2O + XVIII
3·91 C* (4) 0·01 C* (0) 4·04 C* (4)

Kuhn – Roth

Me C*O2H

Me2C*O

Li2C*O3

CHI3
0·97 C* (1)

BaC*O3
0 C* (0)

an esterified 2-hydroxyketone leading directly to a cyclopentane carboxylic acid, and (iii) a rearrangement of a diesterified diequatorial cyclohexane-1:2-diol of a type observed to convert an 11-acetoxy (or tosyloxy)-12-tosyloxy (or acetoxy-) steroid into a C norsteroid,[15] from which a cyclopentane aldehyde would result.

We have been able to confirm the general accuracy of our view of the biosynthesis and to obtain information on the rearrangements involved by degrading gibberellic acid obtained from growth media containing either $CH_3{}^{14}CO_2H$ or (2-^{14}C)-mevalonic lactone. The incorporation of radioactivity was much higher with the latter substrate (2% compared with 0·2%). The degradation methods were essentially those used in the structure determination. The results are expressed as for rosenonolactone in Schemes C and D on p. 245.

The degradations are in quantitative agreement with the formation of gibberellic acid from 4 molecules of mevalonic lactone or 12 molecules of acetic acid. Reference to the predicted labelling patterns XVa and XVb in the diterpene presursor shows clearly that the lactone carbonyl carbon atom is derived specifically from the 3'-position of mevalonic lactone and that the carboxylic carbon of gibberellic acid arises specifically from the 9-position in the cyclic precursor.

The degradations also illuminate the mechanism of formation of the bridged-ring system, a problem discussed already by Wenkert[16] on theoretical grounds in the case of the analogous phyllocladene system. A likely mechanism, as shown in the sequence (XXII) → (XXIII),* is attack of a carbonium ion at the 14-position on the 18:19-double bond of an axial vinyl group (quasi-axial in the non-protonated precursor). The overall result involves migration of $C_{(6)}$ from $C_{(7)}$ to $C_{(18)}$, i.e. the original Me group (becoming $=CH_2$ in the final product) remains attached to a labelled carbon atom if Me^*CO_2H is the precursor. In fact, the Kuhn–Roth oxidation on tetrahydrogibberellic acid confirms this attachment. An alternative, but theoretically much less likely route,[16] shown in XXIV → XXV involves migration of the Me to the $C_{(18)}$ (unlabelled carbon) and is ruled out by this evidence. In phyllocladene biosynthesis the $C_{(14)}$ cation could be produced by protonation of the 8:14-double bond in a rimuene-type precursor; or it could result as in gibberellic acid from a cationoid cyclization of the type shown in VII → XXVI → XXVII.

As with rosenonolactone, no attempt can be made at this stage to indicate the position of oxidation steps in the sequence. In order to explain the presence of the hydroxyl group at the bridge-head it is tempting to postulate an incompletely concerted reaction with intermediate production of a ketone of type XXVIII rearranging to XXIX. There is at present no evidence to distinguish such a scheme from the alternative involving the transformation XXII → XXIII followed by hydroxylation.

The reaction sequence XXX → XXXI is the "obvious" one[17] for the change gibberellic acid into gibberic acid (so far as this part of the molecule is concerned), the reaction being initiated by protonation of the $=CH_2$. Using gibberellic acid derived from $Me^{14}CO_2H$ this conversion would give gibberic acid in which both Me

* These and subsequent perspective diagrams are drawn for diterpene skeletons having the C_{20}-methyl group β, i.e. of the same stereochemical series as cholesterol.

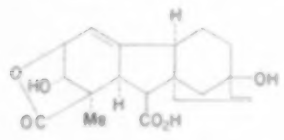
[15] J. B. Bredenberg, *Acta Chem. Scand.* **11**, 927 (1957).
[16] R. F. Hirschmann, H. L. Slates, R. W. Walker and N. L. Wendler, *Chem. & Ind.* 901 (1954).
[16] E. Wenkert, *Chem. & Ind.* 282 (1955).

groups would remain attached to labelled carbon atoms. In fact Kuhn–Roth oxidation gave acetic acid with approximately one half of the expected activity. This result could indicate that the gibberellic–gibberic acid transformation involves migration of the methylene carbon atom (presumably as a methyl group) to an inactive carbon atom. This could possibly occur as a consequence of preliminary hydration of the

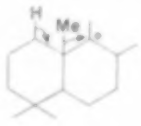
[17] B. E. Cross, J. F. Grove, J. MacMillan and T. P. C. Mulholland, *Chem. & Ind.* 954 (1956).

methylene double bond followed by a pinacol–pinacolone rearrangement XXXII → XXXIII, but this sequence, which implies an intermediate having a carbonium ion centre at the bridgehead position, appears mechanistically improbable. Elucidation of the stereochemical interrelationship between the two acids should settle this point.

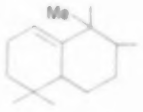
The above verification of the terpenoid character of rosenonolactone and gibberellic acid permits a number of reasonable speculations on the stereochemistry of each metabolite. Infra-red evidence indicates that the lactone carbonyl groups in both substances form part of an unstrained five-membered ring which accordingly must be attached diaxially to the ring system. These groups have been shown to be derived specifically from the 3′-position in mevalonic lactone thus providing circumstantial evidence that the initial diterpene cyclisation is stereochemically similar in both biosyntheses. Enzymic cyclisation of acyclic terpenes is known or believed to give the *trans-anti*-arrangement of the asymmetric centres at the 11-, 12- and 13-positions in diterpenes* (and in analogous positions in triterpenes) and it is reasonable to presume a similar stereochemistry in the precursors of rosenonolactone and gibberellic acid. In the first case the incorporation of an axial carbon substituent in the 1-position into the bridged lactone ring is most simply interpreted as occurring through a concerted reaction involving migration of the methyl group from the 12- to the 13-position as already shown above in VII and VIII. It would therefore be predicted that the stereochemistry of rosenonolactone is represented by Va or a diastereoisomeric structure, provided that later epimerisation at the 14-position (which would be permitted by the adjacent carbonyl group) does not occur. Evidence[18] confirming the stereochemical assignment Va was obtained later. In the case of gibberellic acid the rearrangement for formation of rings C and D which we have demonstrated above defines the stereochemical interrelationships at the 7-, 13- and 14-positions in the diterpene precursor and the stereo-chemistry which would be predicted depends on whether the methyl group attached to the 12-position is oxidized *in situ* or after a migration reaction. In the first case oxidative removal of the methyl group at the 12-position would not be expected to disturb the stereochemistry (cf. lanosterol oxidation) and, taking into account the fact that the hydroxyl in ring A is axial,



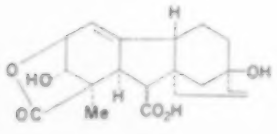
XXXIV



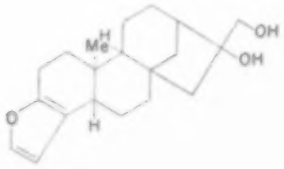
XXXV



XXXVI



XXXVII



XXXVIII

* But see E. Wenkert and J. W. Chamberlain, *J. Amer. Chem. Soc.* **81**, 688 (1959).

[18] B. Green, A. Harris, W. B. Whalley and H. Smith, *Chem. & Ind.* 1369 (1958).

gibberellic acid is defined as XXXIV.* The presence of the double bond in ring A suggests the additional possibility that the methyl group is removed from the 13-position after a migration of the type shown in XXXV and XXXVI. This would involve an inversion at this position and gibberellic acid would then be represented by XXXVII.* It has been suggested[19] that cafestol possesses the structure and absolute configuration XXXVIII (opposite stereochemical series to cholesterol). It is of interest that this structure is consistent with a biosynthesis paralleling the early stages of gibberellic acid synthesis demonstrated here.

VOL. 7 1959

EXPERIMENTAL

General directions are as for Part XIX—Relative molar activities (r.m.a.'s) (a) and (b) refer to labelled metabolites and corresponding degradation products derived from $Me^{14}CO_2Na$ and (2-^{14}C)-mevalonic lactone respectively. Theoretical numbers of labelled carbon atoms and r.m.a.'s refer to the appropriate postulated distributions of radioactivity. Degradation methods for rosenonolactone and gibberellic acid are these of the earlier structural work; only modifications are described in detail. M.p.s. were measured on the Kofler bloch and are uncorrected. Light petroleum means the fraction b.p. 40–60°.

(^{14}C) *Rosenonolactone*

(a) *Trichothecium roseum* Link was grown as previously described. After 4 weeks aqueous $Me^{14}CO_2Na$ (0·25 mc) was distributed between 4 flasks each containing 750 cc of medium. After a further 2 weeks $Me^{14}CO_2Na$ (0·25 mc) was added similarly and growth was allowed to proceed for a total of 8 weeks. The mycelium was harvested in the usual way to give, from benzene–light petroleum, rosololactone (0·25 g) m.p. 184–186°. (Found: r.m.a. × 10^{-4}, 261) and impure rosenonolactone (1·54 g), an aliquot of which was purified (Found: r.m.a. × 10^{-4}, 195). The remainder (1·0 g) was combined with pure unlabelled lactone (6 g) and labelled lactone obtained by carrier extraction of the previously removed fat fraction with pure unlabelled lactone (3 × 0·9 g). Recrystallization from ethanol gave rosenonolactone m.p. 212–214° (20 μc; 4%). (Found: r.m.a. × 10^{-4}, 25·4).

(b) (2-^{14}C) Mevalonic lactone (0·2 mc) was incorporated into the culture medium as for $Me^{14}CO_2Na$, giving rosenonolactone (7·9 μc; 4%). (Found: r.m.a. × 10^{-4}, 9·85).

Ozonolysis of (^{14}C) *rosenonolactone*

The lactone (350 mg) was ozonized in acetic acid (40 cc) at room temp. One seventh of the solution was stirred with zinc dust (150 mg) and water (0·5 cc) for 3 hr. Steam distillation gave formaldehyde obtained as the 2,4-dinitrophenylhydrazone m.p. (from aqueous ethanol) 167–169°. (Found: r.m.a. × 10^{-4}, (a) 3·13; (b) 0.1 C requires (a) 3·18; (b) 2·46). 30% Hydrogen peroxide (3 cc) was added to the remaining ozonolysis solution. After 20 hr excess reagent was decomposed catalytically with palladized charcoal, water was added and the product was collected with ether. The portion which was soluble in aqueous sodium carbonate gave, after recrystallization from aqueous ethanol the acid (X) (172 mg) m.p. 258–260°. (Found: r.m.a. × 10^{-4}, (a) 21·8; (b) 9·65. 7*C, 4*C require respectively (a) 22·3; (b) 9·85).

Decarboxylation of (^{14}C) *rosenonolactone*

(i) The lactone (64 mg) and naphthalene-2-sulphonic acid (20 mg) were maintained at 160° for 10 min (vigorous gas evolution) in a stream of nitrogen. The effluent carbon dioxide was collected as barium carbonate (37 mg, 0·92 mole). (Found: r.m.a. × 10^{-4}, (a) 0; (b) 0·11. 1*C requires (a) 3·18; (b) 2·46). The neutral fraction of the residual oil had a single ν max at 1660 cm^{-1} in the C=O stretching region.

(ii) Isoros-11,12-en-16-oic acid (100 mg) was heated at 250° for 1 hr in a stream of nitrogen. The carbon dioxide was collected as barium carbonate (46 mg, 0·70 mole). (Found: r.m.a. × 10^{-4},

* Or the enantiomer.

[19] M. Cais, C. Djerassi and L. A. Mitscher, *J. Amer. Chem. Soc.* **80**, 247 (1958).

(a) 0; (b) 0·10. 1°C requires respectively (a) 3·18; (b) 2·46). The neutral residue had no carbonyl or hydroxyl absorption in the infra-red.

(^{14}C)-Rosoic acid

Dihydrorosenonolactone (200 mg) was refluxed in 0·5 N ethanolic sodium hydroxide (3 cc) for 30 min. The ethanol was removed under reduced pressure, the volume was made up to 20 cc with water and potassium permanganate (200 mg), sodium carbonate (200 mg) was added portionwise with stirring over 4 hr. After a further 2 hr the solution was acidified and decolorized with sodium sulphite and the product was collected with ether.. The acidic fraction gave, after recrystallization from ethyl acetate–light petroleum, rosoic acid (XI) (170 mg) m.p. 228–230°.

Scission of (^{14}C) rosoic acid

Rosoic acid on retroaldolization gave the ketone (XIII) as an oil assayed as the semicarbazone m.p. (from ethanol) 176–178°. (Found: r.m.a. × 10^{-4}, (a) 12·3; (b) 2·42. 4°C, 1°C require respectively (a) 12·7; (b) 2·46), and the acid (XII) m.p. (from ethyl acetate) 205°. (Found: r.m.a. × 10^{-4}, (a) 12·3; (b) 6·92. 4°C, 3°C require respectively (a) 12·7; (b) 7·38). Kuhn–Roth oxidation of the above semi-carbazone gave acetic acid (1·50, 1·48 moles in replicate experiments) obtained as the lithium salt which was degraded further to $BaCO_3$ (Me). (Found: r.m.a. × 10^{-4}, (a) 0·42; (b) 0·05. 1°C requires (a) 3·18; (b) 2·46) and $BaCO_3$ (CO_2H). (Found: r.m.a. × 10^{-4} (a) 0·38; (b) 0). Kuhn–Roth oxidation of the acid (XIII) gave lithium acetate (0·40, 0·41 mole) further degraded to $BaCO_3$ (Me). (Found: r.m.a. × 10^{-4}, (a) 0; (b) 2·36. 1°C requres (a) 3·18; (b) 2·46) and $BaCO_3$ (CO_2H) (Found: r m.a. × 10^{-4}, (a) 3·080 (b) 0).

Ozonolysis of the ketone (XIII) gave the oily ketoacid (XIV) which with aqueous sodium hypoiodite gave iodoform converted in the usual manner to $BaCO_3$. (Found: r.m.a. × 10^{-4}, (a) 0; (b) 0·04).

Concentrated sulphuric acid (1 cc) was added to the above ketoacid (34 mg) and sodium azide (75 mg) in benzene (3 cc) in a stream of nitrogen. The effluent carbon dioxide was collected as $BaCO_3$ (31 mg., 0·85 mole). (Found: r.m.a. × 10^{-4}, (a) 2·54; 1°C requires (a) 3·18).

(^{14}C) Gibberellic acid

(a) *Gibberella fujikuroi* was cultured in a medium (5 l.) containing glucose and ammonium nitrate, and a solution of $Me^{14}CO_2Na$ (0·5 mc) was added when the glucose was almost exhausted. The crude labelled giberellic acid (0·54 g) was combined with pure acid (6 g) and recrystallized from ethyl acetate–methanol to give (^{14}C) gibberellic acid m.p. 233–235° (0·85 μc; 0·17%). (Found: r.m.a. × 10^{-3}, 58·8).

(b) (2-^{14}C) Mevalonic lactone (0·2 mc) was incorporated as for $Me^{14}CO_2Na$ giving (^{14}C) gibberellic acid (4·8 μc; 2·4%). (Found: r.m.a. × 10^{-3}, 109).

Degradations of (^{14}C) gibberellic acid

(i) Gibberellic acid (300 mg) was converted to gibberic acid (XVI) (230 mg) m.p. 157–159° (Found: r.m.a. × 10^{-3}, (a) 57·8; (b) 106. 8°C, 4°C require respectively (a) 58·8; (b) 109) and barium carbonate (146 mg, 0·85 mole). (Found: r.m.a. × 10^{-3}, (a) 0; (b) 0·53. 1°C requires respectively (a) 7·35; (b) 27·3). Kuhn–Roth oxidation of gibberic acid gave acetic acid (0·62, 0·64 mole), degraded further to $BaCO_3$ (Me). (Found: r.m.a. × 10^{-3}, (a) 0) and $BaCO^3$ (CO_2H). (Found: r.m.a. × 10^{-3}; (a) 3·75. 1°C requires (a) 7·35), and also obtained as *p*-bromophenacylacetate m.p. 86°. (Found: r.m.a. × 10^{-3}, (a) 4·47. 1°C requires (a) 7·35).

(ii) Gibberic acid (220 mg) on dehydrogenation with carbon dixode-free palladium charcoal was converted to gibberone (100 mg) (XIX) m.p. 120–123°. (Found: r.m.a. × 10^{-3}, (a) 57·5; (b) 79·6. 8°C, 3°C require respectively (a) 58·8; (b) 82·0), and barium carbonate (107 mg, 0·70 mole). (Found: r.m.a. × 10^{-3}, (a) 0; (b) 27·5. 1°C requires respectively (a) 7·35; (b) 27·3).

(iii) Gibberellic acid (2·2 g) was converted to allogibberic acid (XVII) (1·14 g) m.p. 200–203°. (Found: r.m.a. × 10^{-3}; (a) 57·3; (b) 107. 8°C, 4°C require respectively (a) 58·8; (b) 109). allo-Gibberic acid (120 mg) was ozonized at room temp in acetic acid (5 cc). Water (2 cc) was added and the solution was stirred with zinc dust (400 mg) for 2 hr. Steam distillation gave formaldehyde, obtained as the 2,4-dinitrophenylhydrazone (60 mg; 0·66 mole) m.p. 167–168°. (Found: r.m.a. × 10^{-3},

(a) 0; (b) 0·29. 1°C requires (a) 7·35; (b) 27·3). The product obtained by extraction of the residue with ether was recrystallized from ethyl acetate–light petroleum to give the ketol (XVIII) (70 mg) m.p. 255–258° (decomp). (Found: r.m.a. $\times 10^{-3}$, (a) 59·9; (b) 110. 8°C, 4°C require respectively (a) 58·8; (b) 109).

Kuhn–Roth oxidation of the ketol (XVIII) gave acetic acid (0·43, 0·50 mole) degraded to $BaCO_3$ (Me). (Found: r.m.a. $\times 10^{-3}$, (a) 0; (b) 26·4. 1°C requires respectively (a) 7·35; (b) 27·3) and $BaCO_3$ (CO_2H). (Found: r.m.a. $\times 10^{-3}$, (a) 7·05; (b) 0).

(iv) Impure gibberic acid (0·67 g) was dehydrogenated with selenium. The impure gibberene (1,7-dimethylfluorene) (0·27 g) in acetone (20 cc) was oxidized with potassium permanganate (900 mg) for 5 hr to yield gibberenone (1,7-dimethylfluorenone) (XXI) (180 mg) m.p. 75–77°. (Found: r.m.a. $\times 10^{-3}$, (a) 51·5; (b) 78·6. 7°C, 3°C require respectively (a) 51·5 (b) 81·9).

(v) Sodium gibberellate (from the acid, 303 mg) in water (5 cc) was shaken with Adam's catalyst (from PtO_2, 80 mg) under hydrogen. Uptake of hydrogen (2·2 moles) was complete in 20 min. Evaporation gave the sodium salt of the acid (XX) which was oxidized by the Kuhn–Roth procedure to acetic acid (1·04 mole), further degradation of which gave $BaCO_3$ (Me) (Found: r.m.a. $\times 10^{-3}$; (a) 0) and $BaCO_3$ (CO_2H). (Found: r.m.a. $\times 10^{-3}$, (a) 7·50. 1°C requires (a) 7·35).

Acknowledgements—We are indebted to members of the staff of I.C.I. Ltd., Akers Research Laboratories, Welwyn, for their most generous co-operation on gibberellic acid. In particular our thanks are due to Mr. G. S. Nixon for growing the mould and providing unlabelled gibberellic acid, and to Mr. J. F. Grove for providing details on degradations before publication. We thank the C.S.I.R.O. (Australia) for the award of an Overseas Research Studentship (to R. W. R.).

VOL. 7 1959

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THE OCCURRENCE OF PROTOCATECHUIC ACID AND ITS 4-O-β-D-GLUCOSIDE IN *BLATTA* AND *PERIPLANETA*

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Abstract—(1) The left colleterial glands of two species of cockroach secrete a β-glucoside of protocatechuic acid, which can be identified readily by chromatography and ultra-violet spectroscopy.

(2) The compound is identical with 4-O-β-D-glucosidoprotocatechuic acid synthesized from 3-O-acetylprotocatechuic acid and 2:3:4:6-tetra-O-acetyl-D-glucosyl-α-bromide.

(3) The ultra-violet spectra of the synthetic and naturally occurring glucosides have been correlated with those of known substituted hydroxybenzoic acids.

THERE are few recorded instances of aromatic glucosides participating in animal metabolic processes. In insects, however, two glucosidic pigments have been described. Hollande[1] showed that a violet glucosidic pigment was present in the fat body of the larva of the beetle *Cionus*; and Brown *et al.*[2] have shown that protoaphins, found in the haemolymph of aphids, are glucosides. In addition, aromatic glucosides have been detected[3] as transient metabolites, being the form in which phenols are detoxified by insects. In a previous publication,[4] evidence was presented for the existence of a β-glucoside of protocatechuic acid in the colleterial or sexual accessory glands of the cockroaches *Blatta orientalis L.* and *Periplaneta americana* (L.)

Both these animals lay eggs in batches of 16 surrounded by a hard brown capsule, known as the ootheca, the walls of which are composed of a quinone-tanned protein, sclerotin. This material, which is of widespread occurrence, particularly in the exoskeletons of invertebrates, was shown by Pryor[5] to be a protein hardened by an *o*-quinonoid substance. Subsequently, Pryor *et al.*[6] isolated protocatechuic acid, the presumed precursor of the quinone, from extracts of cockroach oothecae. The oothecal wall and fluid contents are derived from secretions of the two colleterial glands. The larger left gland contains an abundance of a white, sticky, proteinaceous material; to the small right gland was ascribed[5] the function of secreting protocatechuic acid. Pryor also showed that when isolated tissue of the left gland was incubated with that of the right gland, the contents of the lumen of the former became brittle, brown, and insoluble in dilute mineral acids thus resembling sclerotin. A similar phenomenon was observed[6] when the left gland was incubated with synthetic protocatechuic acid. The presence of this acid in the oothecal fluid has now been confirmed and in addition the fluid is found to contain glucose. However, chromatographic analysis of aqueous or ethanolic extracts of either left or right colleterial failed to reveal the presence of the free acid.[4] When extracts of the left gland

[1] A. C. Hollande, *Arch. Zool. exp. gen.* (Notes et Revues), **51**, 53 (1913).
[2] B. R. Brown, T. Ekstand, A. W. Johnson, S. F. MacDonald and A. R. Todd, *J. Chem. Soc.* 4925 (1952).
[3] C. M. Myers and J. N. Smith, *Biochem. J.* **56**, 498 (1954).
[4] P. C. J. Brunet and P. W. Kent, *Proc. Roy. Soc.* B **144**, 259 (1955).
[5] M. G. M. Pryor, *Proc. Roy. Soc.* B **128**, 378 (1940).
[6] M. G. M. Pryor, P. B. Russell and A. R. Todd, *Biochem. J.* **40**, 627 (1946).

(in contrast to the right gland) were hydrolysed with dilute sulphuric acid, the protocatechuic acid and glucose could be readily detected. Further investigation showed that these two substances could be also obtained by the action of yeast β-glucosidase on extracts of the left gland. We have now synthesized the 4-O-β-D-glucoside of protocatechuic acid and have shown its presence in the left gland of both species of cockroach.

DISCUSSION

The finding of substantial amounts of protocatechuic acid in the oothecal fluid of *Blatta* and *Periplaneta* and in other sclerotized parts of the animals raises the question of its biochemical role, and the form in which such a reactive compound can be stored in the body. It is clear from Pryor's results[5] that a source of this very reactive acid is located in the colleterial glands, but the present investigation has shown that the free acid is not detectable in either right or left colleterial gland. However, when the secretion of the left gland was treated with yeast β-glucosidase, or was subjected to acidic hydrolysis, then the free acid together with D-glucose was found, indicating that the left colleterial gland probably secreted a β-D-glucoside of the acid. The finding that this glucoside, obtained chromatographically from aqueous ethanolic extracts of the left gland was laevorotatory, supported this view.

On the other hand no such substance was present in the right colleterial gland, the secretion of which was found actively to cleave added β-glucosides such as salicin or cellobiose, as well as the glucoside of the left gland. This gland was evidently implicated in the formation of free protocatechuic acid.

The chemical structure of the glucoside of the left gland was then further investigated. Since the glucoside is not readily oxidized in air under alkaline conditions, and gives tests only for monophenols and not for diphenols, it is evident that the glucose moiety is attached to the hydroxyl group at C-3 or C-4. The location of the glucosidic linkage at C-4 has been established by definitive chemical synthesis, and by ultra-violet spectroscopic examination.

The 4-O-β-D-glucoside or protocatechuic acid was synthesized by conventional methods as follows. 3-O-Acetylprotocatechuic acid, prepared by the method of Lesser and Gad,[7] provided a protected starting material. This substance had a strong absorption peak at λ 251 mμ (in ethanol), resembling that of vanillic acid (λ_{max} 260 mμ) and *p*-hydroxybenzoic acid (λ_{max} 251 mμ). The acetyl-derivative was coupled with 2:3:4:6-tetra-O-acetyl-D-glucosyl-α-bromide in the presence of quinoline and silver oxide.[8] This method gave yields markedly superior to several others investigated.[9,10]

Yields were still further improved by starting with 3-O-benzoylprotocatechuic acid and proceeding by an analogous series of reactions. The acetylated glucoside was a crystalline solid ($[\alpha]_D^{19}$-40°), which on deacetylation gave a crystalline product. This had an identical R_F value with the naturally-occurring glucoside, and it was hydrolysed by yeast, and right gland β-glucosidase. In water, the synthetic material had an ultra-violet spectrum identical with the natural product. Further evidence in favour of the 4-O-substituent was obtained by examination of ultra-violet spectra in ethanol,

[7] R. Lesser and G. Gad, *Ber. Dtsch. Chem. Ges.* **59**, 233 (1925).
[8] A. Robertson and R. B. Waters, *J. Chem. Soc.* 2729 (1930).
[9] T. H. Bembry and G. Powell, *J. Amer. Chem. Soc.* **64**, 2419 (1942).
[10] B. Helferich and W. Reischel, *Liebigs Ann.* **533**, 278 (1938).

in M/50 and in M/500 sodium ethoxide. The changes of λ_{min} and λ_{max} in these conditions agree with figures for known[11] substituted hydroxybenzoic acids (Table 1). Glycosidation or methylation of an hydroxyl group in general induces little change in position of λ_{max} (usually a slight hypsochromic shift).

TABLE 1. ULTRA-VIOLET SPECTRA OF 4-O-β-D-GLUCOSIDE OF PROTOCATECHUIC ACID AND OTHER SUBSTITUTED HYDROXYBENZOIC ACIDS

	Solvent	max	min	max
Natural glucoside from left gland	EtOH	238 mμ	266 mμ	290 mμ
	M/50 EtONa	255	275	310
	M/500 EtONa	—	272	292
Synthetic glucoside	EtOH	239	265	289
	M/50 EtONa	241	275	308
	M/500 EtONa	—	274	295
Vanillic acid†	EtOH	260	280	292
	M/50 EtONa	—	245	295
	M/500 EtONa	—	245	295
Isovanillic† acid	EtOH	257	273	293
	M/50 EtONa	257	280	308
	M/500 EtONa	—	272	290

† Values from Dr. T. Swain.

The evidence indicates thus that protocatechuic acid is stored in the form of its 4-O-β-D-glucoside by the left gland which also secretes the protein constituents of sclerotin and a polyphenol oxidase.[12] The right gland secretes a β-glucosidase such that in the intermingled secretions in the genital vestibulum, free protocatechuic acid is liberated. This is oxidized by the polyphenol oxidase to an *o*-quinone which condenses with the available protein ("tanning reaction") to form sclerotin, the resilient and stable material of which the egg-capsule is made.

EXPERIMENTAL

Paper chromatography. Chromatograms were prepared by descending elution on Whatman No. 1 paper using (except where otherwise stated) n-butanol (40%), acetic acid (10%), water (50%) (v/v). Phenols were detected by spraying chromatograms with the following reagents, (i) 1% (w/v) ferric chloride mixed with an equal volume of 1% (w/v) potassium ferricyanide,[13] (ii) 1% (w/v) ferric chloride which gives a green colour with *o*-dihydroxyphenols, becoming pink in NH_4 vapour, (iii) 'chromaffine reagent',[14] i.e. 5% (w/v) solution of KIO_3. This solution gives a yellow or brown colour with dihydroxyphenols. (iv) Pauly's diazo solution[15] i.e. 0·2% (w/v) sulphanilic acid in 0·5

[11] G. H. Mansfield, T. Swain and G. G. Nordstrom, *Nature, Lond.* **172**, 23 (1953).
[12] P. C. J. Brunet, *Quart. J. Micr. Sci.* **93**, 47 (1952).
[13] G. M. Barton, R. S. Evans and J. A. F. Gardner, *Nature, Lond.* **170**, 249 (1952).
[14] L. Lison, *Histochimie Animale* Gautrier-Villars, Paris (1936).
[15] V. Erspamer and G. Boretti, *Arch. Int. Pharmacodyn.* **88**, 295 (1951).

N-HCl (10 vols) mixed with 1% (w/v) sodium nitrite (1 vol) (v) Dihydroxyphenols and other reducing substances were also detected with 5% (w/v) silver nitrate to which 0·88 ammonia solution was added to redissolve the initial precipitate.

Periplaneta americana and *Blatta orientalis* were cultured at 25°. Colleterial glands were dissected under saline from mature adults killed by decapitation. Oothecae were collected at weekly intervals from flower pots filled with moist sand which proved to attract ovipositing females.

Yeast β-glucosidase was supplied by L. Light & Co. Ltd., Colnbrook, Bucks.

Microanalyses were performed by Dr. A. Bernhardt of Mulheim, Ruhr.

VOL. 7 1959

Examination of oothecal fluid

Oothecae were carefully punctured and squeezed in a small screw device so as to express the fluid contained in the space between the eggs and the walls. From 1000 oothecae, 12·8 ml fluid were collected. This had a pink colour, and contained 3·75% (w/v) of dissolved matter; the pH value was 5·6. It gave immediate positive chromaffine and silver nitrate reactions for *o*-dihydroxyphenols and a strong ultra-violet light absorption at 253 mμ. Chromatographic examination of the fluid revealed one principal phenolic constituent (R_F 0·86) identical with protocatechuic acid. Elution of the excised chromatographic spot with 5 ml water gave a solution with absorption spectrum identical with that of protocatechuic acid. Two other phenols (R_F 0·41 and R_F 0·75) were present in the fluid in small quantity; these have not yet been identified. When chromatograms of oothecal fluid were sprayed with aniline hydrogen phthalate[18] a further constituent (R_F 0·18) was revealed. This substance had the same R_F value as glucose in other chromatographic solvents, namely n-butanol, (50%), ethanol (10%), water (40%) (v/v), pyridine (17%), ethyl acetate (33%), water (50%) (v/v). and phenol saturated with water in an atmosphere of NH_3. The sugar was absent in oothecal fluid that had been incubated with washed brewer's yeast at 37° for 5 min. In addition to D-glucose, three minor substances were revealed by aniline hydrogen phthalate having R_F 0·07, 0·10, 0·15. None of these substances has been investigated further.

Examination of extracts of colleterial glands

(i) *Left gland*. The isolated left glands from six animals (each animal provided about 30 mg tissue, wet wt) were homogenized with 0·2 ml ethanol in an all-glass micro-apparatus of the Potter type. Chromatography of the centrifuged extract showed one principal component (R_F 0·57) which gave positive tests for monohydroxyphenols with Pauly's diazo reagent and with ferric chloride/potassium ferricyanide. Tests for dihydroxyphenols were negative (silver nitrate, and chromaffine reagents), as were tests for reducing sugars. In addition, a minor component (R_F 0·41) of unknown composition was present. The major constituent (R_F 0·57) was isolated by elution of several chromatograms with 50% aqueous ethanol, or with water.

(ii) *Right gland*. The glands of six animals (each providing 3 mg tissue, wet wt) were homogenized in 0·1 ml water in the same apparatus as above, and the centrifuged extract was examined chromatographically. Neither in *Blatta* nor in *Periplaneta* could more than trace amounts of phenolic substances be detected. There was no substance (R_F 0·57) comparable to that in the left gland.

Interaction of extracts of right and left glands

A right and a left gland were separately homogenized as above but with water in place of ethanol, centrifuged at 2000 r.p.m. for 5 min and then the supernatant fluids were mixed and incubated at 37° for 1 hr. Chromatograms of the incubated mixture showed the presence of protocatechuic acid (R_F 0·87) (identified by any of the above reagents), and glucose (R_F 0·18). The substance (R_F 0·57) initially present in the left gland disappeared during incubation. No changes were observed when the supernatant fluid of a left gland was incubated alone.

Hydrolysis of left gland extract. The component (R_F 0·57), isolated chromatographically, was non-reducing, laevorotatory and when heated in 0·2 M H_2SO_4 at 100° for 3 hr, it released protocatechuic acid and glucose, identified chromatographically. It appeared therefore to be a β-glucoside.

Action of β-glucosidase on left gland glucoside. 1 mg chromatographically pure glucoside was mixed with 1 mg yeast β-glucosidase and incubated at 37° for 3 hr. In this time, chromatography showed that the glucoside was rapidly hydrolysed to glucose and protocatechuic acid.

[18] S. M. Partridge, *Nature, Lond.* **164**, 443, (1949).

Examination of right gland extracts. 10 mg right gland tissue was homogenized in chilled apparatus with 0·1 ml of water and the extract was centrifuged at 2000 r.p.m. for 5 min. The supernatant solution was incubated at 37° with 0·01 M-salicin (0·1 ml) and the disappearance of the substrate was followed by withdrawal of specimens of the mixture at intervals. Complete hydrolysis of the substrate into glucose and saligenin was observed within 2 hr.

Synthesis of 4-O-β-D-glucopyranoside of protocatechuic acid

(i) 3-*Acetylprotocatechuic acid* (I) was synthesized by the method of Lesser and Gad.[7] The ester had m.p. 198°. (Found: C, 55·0; H, 4·0. Calc. for $C_9H_8O_5$: C, 55·16; H, 4·1%).

(ii) 3-O-*Acetyl*-4-O-β-D-(*tetra*-O-*acetylglucopyranosyl*)-*protocatechuic acid* (II). The above 3-O-acetyl ester (I, 2 g) dissolved in dry quinoline (5 g) was treated with tetra-O-acetylglycosyl-α-bromide (5 g) and dry silver oxide (2 g). The mixture was shaken vigorously for 20 min, during which time the reactants became warm. The mixture was allowed to stand for 1 hr in a vacuum desiccator. It was then extracted with acetic acid (10 ml), and the filtered extract poured into iced water (100 ml). The resulting insoluble crude product was purified either by repeated recrystallization from methanol, or by absorption on charcoal. In the latter procedure, the crude product, dissolved in warm methanol, was stirred with Norite (1 g) and filtered. The charcoal was extracted repeatedly with hot methanol giving (0·2 g) of the *product* (II) as fine white needles, m.p.20 5–206°, $[\alpha]_D^{18}$ −40° ± 2 (*c*, 0·1, $CHCl_3$); light absorption maximum, 252 mμ (methanol). (Found: C, 52·1; H, 5·1. $C_{23}H_{26}O_{14}$ requires: C, 52·4; H, 5·0%).

(iii) 3-O-*Benzoyl*-4-O-β-D-(*tetra*-O-*glucopyranosyl*)-*protocatechuic acid* (III). 3-O-benzoylprotocatechuic acid (1 g, m.p. 110–112°) dissolved in dry quinoline (5 ml) was treated with silver oxide (1·5 g) and tetra-O-acetylglucopyranosyl α-bromide as above. The crude product was readily recrystallized from aqueous ethanol. Yield 0·6 g; m.p. 141–142°, $[\alpha]_D^{28}$ −35° ± 1. (*c*, 0·98, MeOH). (Found: C, 53,8; H, 5·1. $C_{25}H_{28}O_{14}2H_2O$ requires: C, 53·8; H, 5·2%).

(iv) 4-O-β-D-*glucopyranosylprotocatechuic acid* (IV). (a) The above 3-O-acetylglucoside (II, 0·1 g) was de-esterified with a catalytic amount of sodium methoxide in dry methanol as described by Zemplen and Pacsu.[17] Evaporation of the solution yielded a crystalline *product* (IV) which was recrystallized from dry ethanol. Yield 30 mg; m.p. 180–181°, $[\alpha]_D^{28}$ −59° (*c*, 0·1, MeOH), R_F 0·57 in butanol, acetic acid, water; light absorption minima at 228 mμ, 268 mμ, and maxima at 243 and 287 mμ in H_2O. (Found: C, 49·2; H, 5·0. $C_{13}H_{16}O_9$ requires: C, 49·4; H, 5·1%). Incubation of this product (2 mg) with yeast β-glucosidase at 37° results in complete hydrolysis in 45 min.

(b) The same glucoside (IV) was obtained by de-esterification of the benzoyl derivative (III) using the method of Helferich and Reischel.[18]

Acknowledgements—The authors are grateful to Professors Sir Hans Krebs and Sir Alister Hardy for their continued interest, the Agricultural Research Council for support to one of us (P. C. J. B.) and to Dr. T. Swain for helpful suggestions.

[17] G. Zemplen and E. Pacsu, *Ber. Dtsch. Chem. Ges.* **62**, 1613 (1929).

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VOL. 7 1959

RHETSINE AND RHETSININE

THE QUINAZOLINE ALKALOIDS OF *XANTHOXYLUM RHETSA**†

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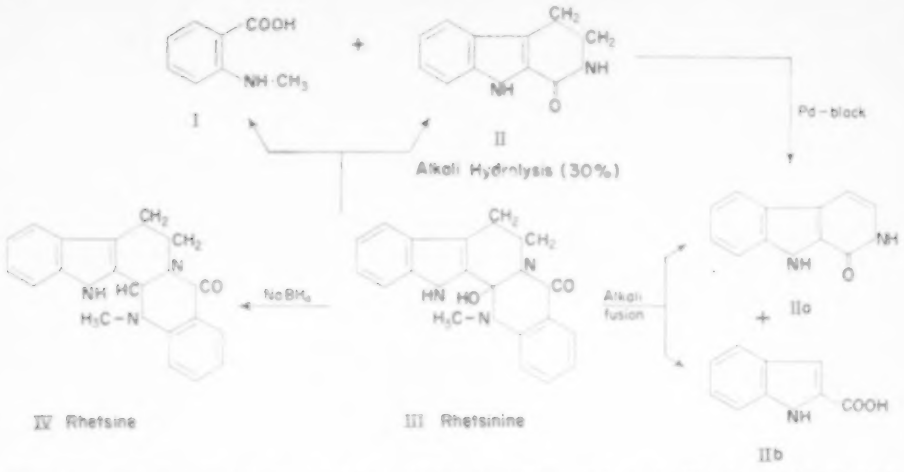
Abstract—From the trunk bark of *Xanthoxylum rhetsa* DC., lupeol and four alkaloids, namely, chelerythrine, rhetine, rhetsine and rhetsinine have been isolated. The constitution of rhetsinine and rhetsine have been established; the former is a new indolequinazoline base, the latter being its desoxy derivative.

THE chemical investigation of *Xanthoxylum rhetsa* DC. (Syn. with *X. budrunga* Wall; Fam. *Rutaceae*) has been undertaken and from the trunk bark of this species four alkaloids *viz.*, rhetsine, $C_{19}H_{17}N_3O$ (yield 0·03%), m.p. 271° (dec), rhetsinine, $C_{19}H_{17}N_3O_2$ (0·05%), m.p. 192° (dec), rhetine (0·01%), m.p. 254° and chelerythrine, $C_{21}H_{19}NO_5$ (0·014%), m.p. 210°, have been isolated in addition to lupeol[1] (0·7%). Rhetsine and rhetsinine are indolequinazoline alkaloids which have been observed so far only in *Evodia rutaecarpa*.[2] The chemistry of rhetsine and rhetsinine is described in the present communication.

Rhetsinine has the molecular formula, $C_{19}H_{17}N_3O_2$ and is a monoacidic tertiary base forming a monomethiodide and only one series of salts with hydrochloric, nitric and picric acids. Rhetsinine yielded a crystalline chloroplatinate. Both the base and its hydrochloride were optically inactive. It contained one iminomethyl and at least one active hydrogen but lacked in methoxyl, methylenedioxy, sidemethyl and carbonyl groups (as indicated from its indifferent behaviour towards carbonyl reagents). Catalytic reduction of rhetsinine furnished a new colourless compound, deoxyrhetsinine, $C_{19}H_{17}N_3O$, m.p. 271° (dec) which was also obtained from the parent base during its reduction with sodiumborohydride. I.R. spectrum of deoxyrhetsinine lacked the peak absorption for hydroxyl at 2·9 μ but retained all other absorption bands discernible in the infra-red spectrum of the original base. These data eventually proved that rhetsinine is a carbinolamine compound. This is in consonance with the analyses of its salts, the latter being formed from the base with a loss of one molecule of water.

Alkaline hydrolysis (30 per cent alcoholic potassium hydroxide) degraded the alkaloid to N-methylanthranilic acid, $C_8H_9NO_2$ (I) and a base, $C_{11}H_{10}N_2O$. The base was dihydropyrid-[3,4-b]-indole-1(2)one[3] (II) was settled by the fact that upon dehydrogenation with palladium black it produced pyrid-[3,4-b]-indole-1(2)-one[4] (IIa). Upon fusion with alkali rhetsinine decomposed into indole-2-acid (IIb) and pyrid-[3,4-b]-indole-1(2)-one (IIa) besides several indolaceous fragments which are under

* Part I in *Xanthoxylum* series.
† This paper is dedicated to Professor P. Karrer on the occasion of his 70th Birthday Celebrations.
[1] A. Chatterjee and C. Ghosh, *Ind. Sci. Congress* 44th Proc. Part III, p. 124.
[2] T. A. Henry: *The Plant Alkaloids* (4th Ed.) p. 498. Blackiston, Philadelphia and Toronto (1949).
[3] R. H. F. Manske and R. Robinson, *J. Chem. Soc.* 240 (1927).
[4] E. Schlittler, H. U. Huber, F. E. Bader and H. Zahnd, *Helv. Chim. Acta* **37**, 1912 (1954).



characterization. Isolation of N-methylanthranilic acid and dihydropyrid [3,4-b]-indole-1(2)-one from alkali hydrolysates of the base and indole-2-acid and pyrid [3,4-b]-indole-1(2)-one from alkali fusion products established the following indole-quinazoline structure III for rhetsinine and IV for deoxyrhetsinine.

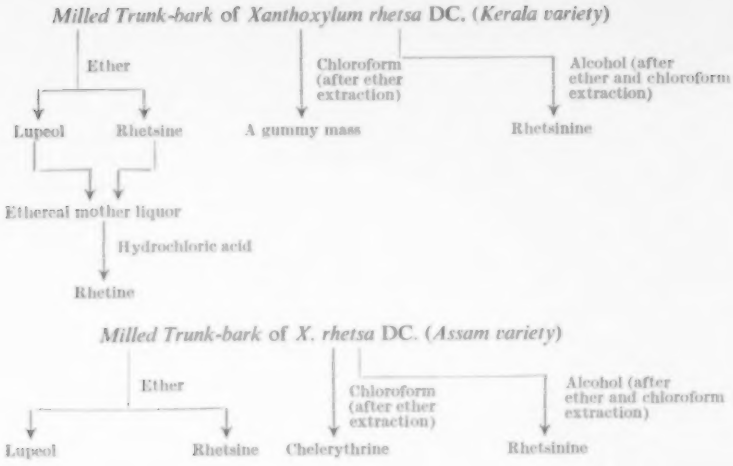
From the elementary analyses, colour reactions and properties (both physical and chemical) rhetsine, $C_{19}H_{17}N_3O$, m.p. 271° (dec) appeared to be identical with deoxyrhetsinine. This was subsequently confirmed from their mixture melting point determination and from a comparison of their U.V. and I.R. spectra. Hence the formulation of rhetsine stands as IV. Thus simultaneous occurrence of rhetsinine and its deoxy-derivative (= rhetsine) in the trunk-bark of *X. rhetsa* appeared to be of great interest from the view point of biogenesis. The constitution of the third alkaloid, rhetine, is in progress. The fourth alkaloid, $C_{21}H_{19}NO_5$ of *X. rhetsa* could be recognized as chelerythrine from its elementary analyses, from an examination of its functional groups and several derivatives as also from the analysis of its dihydro (= deoxy) derivative, $C_{21}H_{19}NO_4$ prepared from the base by reduction with sodium borohydride. The quaternary nature of this alkaloid was revealed from the analysis of its hydrochloride, $C_{21}H_{18}NO_4Cl$, m.p. 210°, and picrate, $C_{21}H_{17}NO_4C_6H_2OH(NO_2)_3$, m.p. 236° (dec), which formed with elimination of a molecule of water. The identity of this alkaloid with chelerythrine could finally be established by a direct comparison of the alkaloid concerned with an authentic sample of chelerythrine and their derivatives.

EXPERIMENTAL*

Isolation. Both Kerala (South India) and Assam (North India) varieties of *X. rhetsa* have been examined. Kerala variety produces rhetsine, rhetsinine and rhetine but no chelerythrine which occurs in Assam species but the latter lacks rhetine.

3 kg milled trunk-bark of *X. rhetsa* was extracted exhaustively with 3 l. ether in a soxhlet for 48 hr. During extraction lupeol and rhetsine (A) deposited in the extraction flask. A further crop of lupeol and rhetsine (B) was obtained from ether concentrate when kept for a fortnight in the frigidaire. Residual ether solution (250 cm³) was diluted with another 300 cm³ ether and shaken with 2 N HCl (50 cm³ × 3) when rhetine, m.p. 238–242° was precipitated. After repeated crystallizations from methanol and ethanol, m.p. of rhetine could be raised to 254°.

* U.V. spectra have been studied in spectral alcohol with Beckman spectrophotometer Model DU. I.R. spectra have been examined in Nujol. For analysis all the samples have been dried in high vacuum at 100° for 12 hr.



The bark materials left after ether extraction were percolated with 3 l. hot chloroform and then refluxed with 3 l. alcohol for 64 hr. Acid extract of chloroform solution of Kerala species gave negative tests for alkaloids but that of Assam sample yielded chelerythrine chloride (C, 0·42 g).

Alcoholic extract of the bark was concentrated to 250 cm³ which was poured into 1 l. water acidulated with 1% acetic acid and left overnight. The clear orange decant was basified with sodium carbonate. The base liberated was taken up in chloroform (75 cm³ × 4). From the chloroform concentrate (50 cm³) rhetsinine separated out in reddish yellow rhombic plates, m.p. 186–190° (dec) which changed to yellow on keeping. After several crystallizations from the same solvent and from a mixture of chloroform and ethanol (1 : 3) pure rhetsinine, m.p. 192° (dec), $[\alpha]_D^{25°} = \pm 0°$ was obtained (1·5 g). It is sparingly soluble in ethanol, methanol, benzene, ethyl acetate, acetone, readily soluble in chloroform, and insoluble in water, dilute acid and alkalies. Thus alkaloid tests of the base could only be performed in conc HCl in which it is soluble. Paper chromatogram of the base was examined on a formamide impregnated paper using n-butanol : hydrochloric acid : water (100 : 1 : 30) ($R_f = 0{\cdot}55$ at 31°) and also n-butanol : formic acid : water (12 : 1 : 7) ($R_f = 0{\cdot}59$ at 31°) as developers. A single fluorescent spot appeared on the chromatogram. (Found: C, 71·47; H, 5·50; N, 13·05; H^+, 0·20; (N)—CH_3, 4·24; mol. wt. 314. (Rast). Calc. for $C_{19}H_{17}N_3O_2$: C, 71·47; H, 5·33; N, 13·16; H^+, 0·30; (N)—CH_3, 4·70%. mol. wt. 319.) The alkaloid was indifferent towards ferric ion and Tollens reagent, and does not reduce Fehling's solution. It turned deep yellow with conc H_2SO_4, greenish yellow with conc HNO_3, light yellow with Fröhde's reagent. U.V.: λ_{max} 314 mμ (log ε 4·15). I.R.: 2·9 (—OH), 3·03 (—NH), 5·9 (amide) and 6·03 μ (phenyl nucleus).

Rhetsinine chloride. 30 mg base in 10 cm³ chloroform was treated with 0·5 cm³ 2 N HCl and shaken vigorously, when hydrochloride of the base separated in yellow flocky mass. It crystallized from ethanol in yellow needles, m.p. 228–229°, (dec) $[\alpha]_D^{25°} = \pm 0°$. (Found: N, 12·44; Cl, 10·52. Calc. for $C_{19}H_{16}N_3OCl$: N, 12·51; Cl, 10·88%.)

Rhetsinine methiodide. 2 cm³ methyliodide was added to 30 mg base in 10 cm³ chloroform and kept overnight when long yellow slender needles of methiodide of the base separated. It was further purified by crystallization from ethanol, m.p. 220–221° (dec). (Found: N, 9·48. Calc. for $C_{20}H_{20}N_3O_2I$: N, 9·11%.)

Rhetsinine nitrate. 25 mg base hydrochloride in 20 cm³ ethanol was treated with 4 N HNO_3 till the precipitation was complete. The nitrate crystallized from ethanol in light-orange yellow needles, m.p. 242–243° (dec). (Found: N, 15·79. Calc. for $C_{19}H_{16}N_4O_4$: N, 15·39%.)

Rhetsinine picrate. 30 mg base hydrochloride was dissolved in 12 cm³ water in which 30 mg picric acid in 5 cm³ water was slowly added. The precipitated yellow picrate crystallized from ethanol in orange-yellow slender needles, m.p. 270–272° (dec). (Found: N, 15·27. Calc. for $C_{25}H_{20}N_6O_9$: N, 15·31%.)

Rhetsinine chloroplatinate. 80 mg base hydrochloride was dissolved in 50 cm³ hot water. The solution was cooled and treated with 5% chloroplatinate solution with stirring till the precipitation

was complete. The bright orange crystalline chloroplatinate was too sparingly soluble to be crystallized from any solvent. A pure sample when heated charred at 230° without melting. (Found: Pt, 19·05. Calc. for $(C_{19}H_{17}N_2O_2)_2$. H_2PtCl_6: Pt, 18·60%.)

Sodium borohydride reduction of rhetsinine. 1·0 g rhetsinine was dissolved in 150 cm³ chloroform–ethanol mixture (1 : 2). To this orange-yellow solution, 600 mg finely powdered sodium borohydride was added. There was copious evolution of hydrogen and the solution became colourless. Deoxyrhetsinine slowly separated after some time. It was left overnight at ordinary temp. Excess of the solvent was removed. The residue was treated with 50 cm³ water and extracted exhaustively with 500 cm³ chloroform. The chloroform extract after being distilled left a colourless solid (700 mg) which crystallized from chloroform–ethanol mixture in shining rectangular plates m.p. 270–271° (dec), $[\alpha]_D^{25°} = \pm 0°$. Deoxyrhetsinine turned red colouration with conc H_2SO_4, red to deep brown with conc H_2SO_4 and potassium dichromate, orange-red with Fröhde's reagent, red with conc H_2SO_4 and ceric sulphate, conc H_2SO_4 and *p*-dimethylaminobenzaldehyde, conc HNO_3, conc H_2SO_4 and ammonium molybdate and pink to violet with vanillin and conc HCl. (Found: C, 74·61; H, 6·00; N, 13·88; (N)—CH_3, 5.00; H^+, 0·30. Calc. for $C_{19}H_{17}N_3O$: C, 74·75; H, 6·22; N, 13·77; (N)—CH_3, 4·91; H^+, 0·33%.) U.V.: λ_{max} 266 mμ (log ε 4·08), 312 mμ (log ε 4·08) and 324 mμ (log ε 3·29). Deoxyrhetsinine is found to be identical with rhetsine, m.p. 271° (dec), another alkaloidal constituent of *Xanthoxylum rhetsa* DC., from an examination of their mixed m.p., U.V. and I.R. spectra.

Catalytic hydrogenation of rhetsinine. 220 mg rhetsinine dissolved in 25 cm³ glacial acetic acid was hydrogenated in presence of 70 mg Adam's platinum oxide catalyst for 9 hr at 28°. The uptake of hydrogen was slow and at the end it consumed only 20 cm³ hydrogen. The acetic acid was removed under reduced pressure and the concentrate was cooled to 0° and poured in 25 cm³ water. The resulting turbid solution was basified when a light yellow flocculent precipitate separated which was taken up in 50 cm³ chloroform. The latter upon concentration and dilution with ethanol produced yellowish brown solid melting at 245–253° (dec). From chloroform–ethanol mixture (1 : 2) it separated in rectangular colourless plates, m.p. 265–267° (80 mg). Further crystallization from methanol–acetone mixture raised the m.p. to 271° (dec). It was found to be identical with deoxyrhetsinine prepared from the base by reduction with sodium borohydride.

Alkali hydrolysis of rhetsinine. 2·0 g rhetsinine was boiled under reflux with 75 cm³ 30% alcoholic caustic potash for 5 hr. The pale yellow hydrolysate was distilled under reduced pressure to remove ethanol, when a yellow oil separated. This was diluted with 25 cm³ water and extracted with 300 cm³ ether. The aqueous portion (P) was kept. The ethereal extract was washed with water, dried and concentrated when dihydropyrid-[3,4-b]-indole-1(2)-one was obtained (30 mg). The compound melted at 172° and gave a blue-violet colour with Fröhde's reagent and a dark-brown colour with $K_2Cr_2O_7$ and conc H_2SO_4, reminiscent of a β-carboline compound. (Found: C, 71·10; H, 5·49; N, 15·20. Calc. for $C_{11}H_{10}N_2O$: C, 70·96; H, 5·37; N, 15·05%.)

Conversion of dihydropyrid-[3,4-b]*-indole-*1(2)*-one into pyrid-*[3,4-b]*-indole-*1(2)*-one.* 20 mg substance was intimately mixed up with 100 mg palladium black and the mixture was heated in a distillation bulb at 190–195° for 45 min. It was then sublimed *in vacuo* at 160°/0·01 mm when a solid mass was obtained. This was twice crystallized from benzene when silky colourless needles, m.p. 259°, separated. (Found: C, 71·59; H, 4·21; N, 14·98. Calc. for $C_{11}H_8N_2O$: C, 71·73; H, 4·34; N, 15·21%.)

Isolation of N-methylanthranilic acid. The aqueous alkaline solution (P; *vide supra*) left after ether extraction of alkali hydrolysates was cooled and carefully acidified with dil acetic acid. A yellowish-white precipitate appeared at pH 6 which was taken up in 300 cm³ ether. The ethereal layer which exhibited a strong bluish-violet fluorescence was washed, dried and concentrated when a yellowish product was obtained. It crystallized from petroleum ether (B.P. 40–60°) and absolute ethanol mixture (2 : 1) in colourless needles, m.p. 179–180° (750 mg). (Found: C, 63·45; H, 6·01; N, 9·36. Calcd. for $C_9H_9NO_2$: C, 63·57; H, 5·96; N, 9·27%.) This did not depress the melting point of an authentic sample of N-methylanthranilic acid on admixture.

Alkali fusion of rhetsinine. 500 mg rhetsinine was fused with 3·5 g caustic potash in a nickel crucible heated to 300–310° for 15 min. The fused mass was well stirred to prevent the frothing up of the molten mass due to the copious evolution of gases possessing an indolaceous odour. It was cooled, lixivated with 20 cm³ water, 2·0 g solid NH_4Cl was added and the resulting solution was extracted exhaustively with ether. The ether extract containing basic and neutral fractions was

freed from the solvent and the residue on sublimation *in vacuo* at 0·01 mm gave two different fractions (X) at 66–80° and (Y) at 150–160°. Fraction (X) had a faecal smell and consisted of a few drops of reddish-yellow oil. It gave a positive pine chip test for indole. Fraction (Y) solidified on keeping. This on being crystallized from benzene deposited fine needles, m.p. 259°, proved to be identical with pyrid-[3,4-b]-indole-1(2)-one by mixed melting point and analysis. (Found: C, 71·64; H, 4·45; N, 15·01. Calc. for $C_{11}H_8N_2O$: C, 71·73; H, 4·34; N, 15·21%.)

Isolation of indole-2-carboxylic acid. The aqueous alkaline solution left after the removal of basic and neutral fractions from alkali fusion products was acidified and extracted with 200 cm³ ether. The ether extract on being washed with water, dried and distilled left a semi-solid residue. It was heated *in vacuo* at 0·01 mm when fine needles sublimed at 80–110°. This was further purified by several crystallizations from a mixture of petroleum ether (B.P. 40–60°) and ether and finally from benzene when shining flakes m.p. 199–200° were obtained (40 mg). (Found: C, 67·12; H, 4·45; N, 8·82. Calc. for $C_9H_7NO_2$: C, 67·08; H, 4·34; N, 8·69%.) The acid did not depress the m.p. of an authentic sample of indole-2-carboxylic acid when mixed.

Isolation of rhetsine and lupeol from fractions (A) and (B). The yellow crude solid (36 g) obtained from fractions (A) and (B) (*vide* p. 4) was dissolved in a large volume of ethanol by refluxing. The alcoholic solution on being concentrated and cooled deposited rhetsine. This was purified by several crystallizations from a mixture of chloroform and ethanol (1 : 2) when shining colourless rectangular plates, m.p. 270–271° (dec), $[\alpha]_D^{25°} = \pm 0°$ were obtained (0·9 g). It was sparingly soluble in ethanol, acetone, benzene, ether, ethyl acetate and methanol and insoluble in dilute acids and alkalies. (Found: C, 75·25; H, 5·53; N, 13·88; (N)—CH_3, 5·00; H, 0·30; mol. wt. 305. Calc. for $C_{19}H_{17}N_3O$: C, 75·24; H, 5·6; N, 13·86; (N)—CH_3, 4·91; H^+, 0·33%; mol. wt. 303.)

The alcoholic mother liquor left after separation of rhetsine was concentrated to a small volume to obtain crude lupeol (21 g). It was further purified by chromatography over alumina and subsequent crystallization from benzene and alcohol. The analytical sample melted at 212–213° and responded to Lieberman Burchard test. (Found: C, 84·50; H, 11·93. Calc. for $C_{30}H_{50}O$: C, 84·50; H, 11·73%.) Lupeol produced a crystalline acetyl derivative, m.p. 216–217°. Both lupeol and its acetate did not depress the m.p. of an authentic sample of lupeol and its acetyl derivative.

Chelerythrine. Chelerythrine was prepared by addition of sodium carbonate to an aqueous solution (100 cm³) of the chelerythrine chloride (C), (*vide* p. 5). From ethanol and methanol it formed very pale yellow leaflets, m.p. 210° (300 mg). (Found: C, 69·46; H, 5·60; N, 3·89; —OCH_3, 17·20. Calc. for $C_{21}H_{19}NO_5$: C, 69·10; H, 5·20; N, 3·83; —OCH_3, 16·90%.) It gave positive Labat test.

Chelerythrine chloride. 100 mg chelerythrine was dissolved in 10 cm³ 2 N HCl solution upon warming. On cooling golden-orange needles of chelerythrine chloride, m.p. 203–206° separated out. Repeated crystallizations from ethanol raised its melting point to 210° (dec). (Found: C, 65·48; H, 4·82; N, 3·76. Calc. for $C_{21}H_{18}NO_4Cl$: C, 65·71; H, 4·68; N, 3·65%.)

Chelerythrine picrate. The picrate was prepared by adding a saturated solution of aqueous picric acid to an aqueous solution (20 cm³) of the hydrochloride (50 mg). The yellow picrate separated crystallized from ethanol in fine needles, m.p. 236° (dec). (Found: N, 9·81. Calc. for $C_{27}H_{20}N_4O_{11}$: N, 9·72%.)

Deoxychelerythrine. 100 mg of chelerythrine chloride was dissolved in 50 cm³ methanol in which 1·0 g of sodium borohydride was added and left overnight. The solution gradually turned pale yellow and became colourless. The methanolic solution was freed from the solvent and the residue was treated with 25 cm³ water and shaken with chloroform. The chloroform layer was washed with water, dried over anhydrous sodium sulphate and distilled. The residue crystallized from ethanol in colourless needles, m.p. 165–166°. (Found: C, 72·11; H, 5·31; N, 4·14. Calc. for $C_{21}H_{19}NO_4$: C, 72·20; H, 5·4, N, 4·01%.)

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CHEMISTRY OF THE PODOCARPACEAE—III*

A NEW LIGNAN, SECO-ISOLARICIRESINOL AND FURTHER CONSTITUENTS OF THE HEARTWOOD OF *PODOCARPUS SPICATUS*

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(*Received* 5 *May* 1959)

Abstract—A new lignan for which the name seco-isolariciresinol is proposed, has been isolated from the heartwood of *Podocarpus spicatus*. The structure has been shown to be 2:3-bis(4′-hydroxy-3′-methoxybenzyl)-butan-1:4-diol (II, R = H), and confirmed by an absolute synthesis from (−)-matairesinol (I, R = H). A further examination of the extractives of the heartwood has resulted in the isolation of the minor constituents, (+)-taxifolin, (+)-aromadendrin, kaempferol and sequoyitol, in addition to the previously reported compounds, matairesinol, α-conidendrin, quercetin, genistein and podospicatin.

Previous investigations of the constituents of *Podocarpus spicatus* have shown the presence, in the heartwood or heartshakes, of the lignans, matairesinol,[1–4] and conidendrin.[5,6] A third constituent, podospicatin, m.p. 212°,[2,3,7] has recently been shown to be 2′:5:7-trihydroxy-5′:6-dimethoxyisoflavone.[4,8] The isolation of quercetin[8] from the heartshakes and genistein[4] from the heartwood has also been reported.

In the present communication, a complete re-examination of the heartwood constituents is reported. In order to facilitate the isolation of minor constituents the concentrate from a methanolic extract was intimately mixed with Celite and successively re-extracted with solvents of increasing polarity. The concentrate from each extract, where possible, was fractionally crystallized and non-crystalline residues fractionated with aqueous alkalies of increasing basicity. Liberal use was made of paper chromatographic techniques to monitor each purification step and for initial indentification of the constituents. The scheme of extraction and the products isolated from each extract shown in Table 1.

By these means the following previously reported compounds were isolated and identified by comparison with authentic samples: matairesinol (2·26% yield), α-conidendrin (0·005% yield), quercetin (0·83% yield), genistein (0·05% yield) and podospicatin (0·13% yield). In addition the following compounds not previously detected in *Podocarpus spicatus* were isolated: (+)-taxifolin (0·002% yield), (+)-aromadendrin (0·001% yield), kaempferol (0·002% yield), sequoyitol (0·009% yield) and a new lignan (0·012% yield).

* Part II: L. H. Briggs and T. P. Cebalo, *Tetrahedron* **6**, 145 (1959).

[1] T. H. Easterfield and J. Bee, *J. Chem. Soc.* **97**, 1028 (1920).
[2] L. H. Briggs, D. A. Peak and J. L. D. Woolloxall, *J. Proc. Roy. Soc. N.S.W.* **69**, 61 (1935)
[3] R. D. Haworth and T. Richardson, *J. Chem. Soc.* 633 (1935).
[4] L. H. Briggs and T. P. Cebalo, *Tetrahedron* **6**, 145 (1959).
[5] R. D. Haworth, T. Richardson and G. Sheldrick, *J. Chem. Soc.* 1576 (1935).
[6] L. H. Briggs and D. A. Peak, *J. Chem. Soc.* 724 (1936)
[7] H. V. Brewerton, *New Zealand J. Sci.* **1**, 220 (1958).
[8] L. H. Briggs and B. F. Cain, *Tetrahedron* **6**, 143 (1959).

TABLE 1. *Podocarpus spicatus* HEARTWOOD EXTRACTIVES

HEARTWOOD

Extracted with methanol

Extract on Celite

Light petroleum extract	Benzene extract	Ether extract	Chloroform extract	Ethyl acetate extract	Butan-1-ol extract
(i) *crystallization* podospicatin (ii) *chromatography* matairesinol	(i) *crystallization* matairesinol podospicatin (ii) Na_2CO_3 *solubles* podospicatin (iii) 4% NaOH *solubles* matairesinol	(i) *crystallization* matairesinol podospicatin genistein quercetin (ii) $NaHCO_3$ *solubles* (+)-taxifolin (+)-aroma-dendrin (iii) Na_2CO_3 *solubles* podospicatin genistein quercetin kaempferol (iv) 0·2% NaOH *solubles* matairesinol seco-isolari-ciresinol (v) 4% NaOH *solubles* matairesinol	(i) *crystallization* matairesinol (ii) Na_2CO_3 *solubles* seco-isolari-ciresinol podospicatin genistein quercetin kaempferol (iii) 0·2% NaOH *solubles* seco-isolari-ciresinol (iv) 4% NaOH *solubles* matairesinol α-conidendrin	(iii) Na_2CO_3 *solubles* quercetin kaempferol (ii) 4% NaOH *solubles* matairesinol	(i) *water solubles* sequoyitol

The new lignan, isolated from the ether and chloroform extracts, is a laevorotatory crystalline solid, m.p. 112·5–113·5°, which gives a positive ferric chloride reaction. The compound has the formula, $C_{20}H_{26}O_6$, and a Zeisel determination shows the presence of two methoxyl groups. The infra-red spectrum shows hydroxyl stretching at 3448 cm^{-1}, phenolic deformation in the regions 1200 cm^{-1} and 1410–1310 cm^{-1} and a band compatible with primary hydroxyl deformation at 1050 cm^{-1}.[9]

Difficulty was experienced in crystallizing acyl derivatives of the lignan. The presence of four hydroxyl groupings was demonstrated, however, by the formation of a tetra-acetate and a tetra-benzoate. The acetate was obtained only as a glass on acetylation in pyridine solution or with fused sodium acetate while the benzoate was obtained as a microcrystalline mono-hydrate by purification from aqueous methanol. Both derivatives showed no hydroxyl absorption in the infra-red.

Two of the hydroxyl groups present in the lignan were shown to be phenolic by the formation of a di-O-methyl ether, $C_{22}H_{30}O_6$, by methylation in aqueous alkali. This derivative had a constant melting point 59–60° when initially crystallized from aqueous methanol but crystallization from chloroform–light petroleum raised the melting point to 120–123°. Prolonged methylation with dimethyl sulphate and potassium carbonate in boiling acetone gave a further di-O-methyl ether, m.p. 120·5–121°, depressed on admixture with the former derivative and which showed major differences in the infra-red spectrum. The formula of the latter derivative, $C_{22}H_{28}O_5$, and the absence of hydroxyl absorption in the infra-red spectrum suggested that it was derived

[9] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (2nd Ed.) p. 95. Methuen, London (1958).

from the former by the loss of the elements of water. That this was so was subsequently shown by dehydration of the former derivative, $C_{22}H_{30}O_6$, to the latter compound with potassium hydrogen sulphate.

Comparison of the ultra-violet spectrum with those of the lignans, matairesinol, α-conidendrin and isolariciresinol (Fig. 1), indicated a close relationship with this

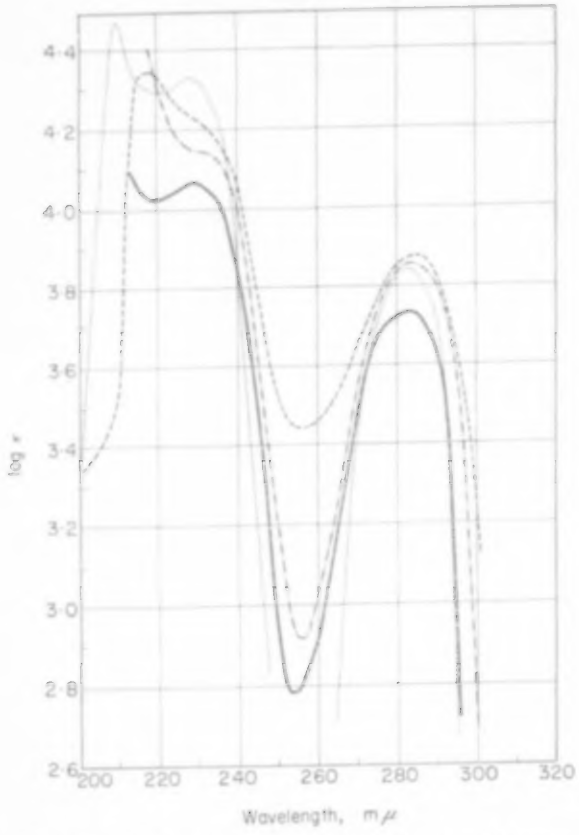
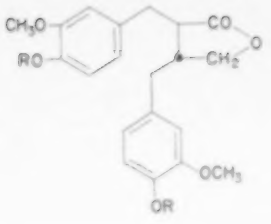


Fig. 1. Ultra-violet spectra of seco-isolariciresinol (II: R = H) . . . . . , matairesinol (I: R = H) ———, isolariciresinol - - - - - -, and conidendrin (VIII) ———

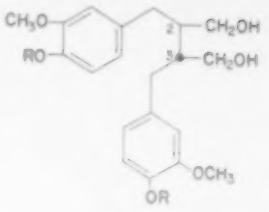
class of compound. Since all the oxygen functions are accounted for by two methoxyl and four hydroxyl groups, the formula, $C_{20}H_{26}O_6$, is only compatible with a lignan possessing a fully saturated aliphatic portion, with two aliphatic hydroxyl groups capable of dehydration. On the assumption that the substitution pattern in the aromatic nuclei is of the common 3-methoxyl-4-hydroxyl type,* and on phytochemical grounds† the lignan can be formulated as (—)-2:3-bis(4′-hydroxy-3′-methoxybenzyl)-butan-1:4-diol (II, R = H).

* Cf. the co-occurring lignans, matairesinol (I, R = H) and α-conidendrin.

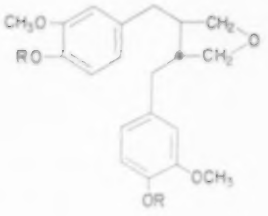
† For reviews of the naturally occurring lignans see W. M. Hearon and W. S. MacGregor, *Chem. Rev.* **58**, 957 (1955); H. Erdtman in *Modern Methods of Plant Analysis* Vol. III, p. 428. Springer-Verlag, Berlin (1955).



I



II



III

The lignan has not been previously isolated from natural sources or prepared synthetically but has been detected by paper chromatography among the hydrogenation products of pinoresinol.[10] To indicate the structural relationship to isolariciresinol, the name seco-isolariciresinol* is proposed for the new lignan. Support for the formulation was obtained by the correspondence of the melting point of the di-O-methyl ether, $C_{22}H_{30}O_6$ m.p. 120–123°, with that recorded by Schrecker and Hartwell for (−)-2:3-diveratryl-butan-1:4-diol (II, R = OCH_3).[11] The di-O-methyl ether, $C_{22}H_{28}O_5$, m.p. 120·5–121°, was obviously the anhydro derivative of the former, formed by ready dehydration of the diol grouping[11] by anhydrous potassium carbonate used during the reaction. The melting-point of the anhydro derivative again showed close agreement with the corresponding synthetic derivative, 3:4-bis(3′:4′-dimethoxybenzyl) tetrahydrofuran (III, R = OCH_3) recorded by the above workers. The infra-red spectra of both the di-O-methyl derivatives of the natural products, however, did not have point for point identity with those recorded for the optically active synthetic derivatives.[11,12]

In order to carry out a direct comparison, 2:3-diveratryl-butan-1:4-diol was prepared from (−)-dimethylmatairesinol (I, R = OCH_3) by Haworth and Wilson's method[13] and it in turn dehydrated to the tetrahydrofuran derivative (III, R = OCH_3).[11,13,14] Each of the di-O-methyl derivatives of the naturally occurring lignan showed no melting point depression when mixed with their corresponding synthetic analogues and their corresponding infra-red spectra were identical.

* The prefix *seco* was originally used in the steroid field [Editorial Report on Nomenclature, *J. Chem. Soc.* 3535 (1957)], to denote ring fission with the addition of two hydrogen atoms to the two terminal groups, but has been extended with the same meaning by workers to other fields, e.g. W. H. Evans, A. McGookin, L. Jurd, A. Robertson and W. R. N. Williamson, *J. Chem. Soc.* 3510 (1957).

[10] K. Freudenberg and L. Knof, *Chem. Ber.* **90**, 2857 (1957).
[11] A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.* **77**, 432 (1955).
[12] A. W. Schrecker, *J. Amer. Chem. Soc.* **79**, 3823 (1957).
[13] R. D. Haworth and L. Wilson, *J. Chem. Soc.* 71, (1950).
[14] R. D. Haworth and D. Woodcock, *J. Chem. Soc.* 1054 (1939).

The structure of seco-isolariciresinol was further confirmed by an absolute synthesis from (−)-matairesinol (I, R = H). Reduction by lithium aluminium hydride of the dibenzyl derivative of (−)-matairesinol (I, R = $C_6H_5CH_2$), by Schrecker and Hartwell's method[11] for lactonic lignans, gave the diol (II, R = $C_6H_5CH_2$). Hydrogenolysis of the diol with palladium-charcoal gave 2:3-bis(4′-hydroxy-3′-methoxybenzyl)-butan-1:4-diol (II, R = H), identical in all respects (m.p. and mixed m.p., optical rotation, infra-red spectrum) with seco-isolariciresinol.

The absolute configuration of (−)-matairesinol has been established as 2L, 3D (I, R = H).[15–18] Since the synthesis of seco-isolariciresinol from (−)-matairesinol only involves the reduction of the potential carboxyl group to a primary alcoholic group it follows that the new lignan must have the same absolute configuration, provided the asymmetry at C_2 is preserved. As reduction with lithium aluminium hydride of a carbonyl group adjacent to an asymmetric centre does not affect the symmetry[19] and as benzylation and debenzylation would also not be expected to affect the asymmetry, the synthesis leads to the absolute configuration of seco-isolariciresinol as 2L, 3D (II, R = H).

EXPERIMENTAL

Analyses were by Dr. A. D. Campbell and associates, University of Otago, New Zealand. Infra-red spectra were measured as KBr disks with a Beckmann IR2 instrument and ultra-violet spectra in EtOH solutions with a Beckmann DU instrument. Ultra-violet spectral shifts were measured by the methods of Jurd and co-workers.[20–22] Circular paper chromatography of phenolic constituents was carried out on Whatman's No. 1 paper (24 cm) with the following solvent systems: (A) 60% aqueous acetic acid, (B) phenol saturated with water at 20°. The positions of spots were shown with either 1% alcoholic ferric chloride or diazotized *p*-nitroanaline spray reagents. Light petroleum was of b.p. 50–60°.

Extraction of Podocarpus spicatus *heartwood.* Continuous extraction (Soxhlet) of the finely ground wood (9·3 kg) with 80% aqueous methanol for 56 hr and removal of the solvent *in vacuo* gave a black tar (1·5 kg). After the addition of a little hot methanol the tar was intimately mixed with Celite (1·1 kg) and the friable solid, obtained on drying, successively re-extracted (Soxhlet) with light petroleum, benzene, ether, chloroform, ethyl acetate, butan-1-ol and finally methanol. The residues from each extract, with the exception of the light petroleum and methanol extracts, were purified directly, where possible, by fractional crystallisation from 60% acetic acid. Non-crystalline residues were then fractionated in a suitable solvent between saturated sodium hydrogen carbonate, 10% sodium carbonate, 0·2% sodium hydroxide and 4% sodium hydroxide solutions. Residues from the light petroleum extract were chromatographed directly in benzene on alumina (Brockman, grade III). No crystalline products were isolated from the methanol extract by any purification procedures attempted.

Lignans

Matairesinol. Matairesinol (total yield 210·5 g), m.p. and mixed m.p. 117–118° (identical infra-red spectrum), was isolated by fractional crystallisation of the benzene, ether and chloroform extracts and from the sodium hydroxide fractions from these extracts and the ethyl acetate extract. It was also isolated in trace amount by elution of the light petroleum extract from the column with benzene–ether mixtures.

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VOL. 7 1959

α-Conidendrin. α-Conidendrin, m.p. and mixed m.p. 240–244°* (identical infra-red spectrum), was isolated in small yield (500 mg) from the 4% sodium hydroxide fraction of the chloroform extract by fractional crystallisation from aqueous acetic acid or from ethanol.

seco-isoLariciresinol. Water extraction of the residues from the 0·2% sodium hydroxide fractions of the ether and chloroform extracts and of the sodium carbonate fraction of the chloroform extract gave colourless needles of *seco-isolariciresinol* (1·13 g). After recrystallization from water or dilute alcohol as rods it had m.p. 112·5–113·5°, $[\alpha]^{25}$ −35·6° (*c*, 1·07 in Me_2CO) (Found: C, 66·3; H, 7·2; OMe, 17·0. $C_{20}H_{26}O_6$ requires: C, 66·3; H, 7·2; 2O Me, 17·1%), λ_{max} 209 mμ (log ε 4·5), 229 mμ (log ε 4·3) and 283 mμ (log ε 3·9). Infra-red spectrum: 3436, 3165, 2915, 1608, 1515, 1471, 1458, 1433, 1385, 1359 (Sh.), 1339, 1312, 1272, 1241, 1199, 1189, 1155, 1129, 1120, 1098, 1064, 1050 (Sh.), 1036, 1007, 977, 947, 937, 919, 910, 897, 844, 808, 798 and 744 cm^{-1}.

*seco-iso*Lariciresinol is sparingly soluble in cold water, ether and chloroform but readily soluble in methanol, ethanol and acetone. A concentrated solution gave a green colour with alcoholic ferric chloride.

Tetra-O-acetyl-seco-isolariciresinol. Acetylation of seco-isolariciresinol with acetic anhydride–pyridine (1 hr; 100°) or with acetic anhydride–fused sodium acetate (2 hr; 100°) and isolation of the products by pouring onto crushed ice, in each case gave an oil which could not be obtained as a solid from any of the normal organic solvents. After chromatography in ethyl acetate on neutralized alumina the *tetra-acetate* was obtained as a colourless glass, b.p. 348° (micro method), which could not be induced to crystallize (Found for sample dried at room temp: C, 62·6; H, 6·7; Ac, 29·2. $C_{28}H_{34}O_{10}$ requires: C, 63·4; H, 6·5; 4Ac, 32·5. $C_{28}H_{34}O_{10}\cdot\frac{1}{2}H_2O$ requires: C, 62·3; H, 6·5; 4 Ac, 31·9%).

Tetra-O-benzoyl-seco-isolariciresinol. Benzoylation of seco-isolariciresinol with benzoyl chloride–pyridine (1 hr; 100°) and isolation of the product by pouring onto crushed ice gave the *tetra-benzoate* which was obtained as a colourless microcrystalline mono-hydrate, m.p. 55–57°, from aqueous methanol (Found, for sample dried at room temp; C, 72·3: H, 5·4. $C_{48}H_{42}O_{10}\cdot H_2O$ requires: C, 72·4; H, 5·6%).

*Mono-O-*3:5-*dinitrobenzoyl-seco-isolariciresinol.* Treatment of seco-isolariciresinol with 3:5-dinitrobenzol chloride (2 fold excess)-pyridine (1 hr; 100°) and isolation of the product in the usual manner gave a gum from which the *mono-*3:5-*dinitrobenzoate*, was obtained as a microcrystalline powder, m.p. 115–118°, from aqueous acetic acid (Found: C, 58·4; H, 5·1. $C_{27}H_{28}O_{11}N_2$ requires: C, 58·3; H, 5·2%). The infra-red spectrum showed strong hydroxyl absorption at 3086 cm^{-1}.

Di-O-methyl-seco-isolariciresinol (II, R = OCH_3). Dimethyl sulphate (1 ml) was added dropwise to a solution of seco-isolariciresinol (150 mg) in 2 N sodium hydroxide solution (5 ml) and the mixture heated on the steam-bath for 1 hr. Repeated crystallization of the resulting gum from aqueous methanol gave *di-*O-*methyl-seco-isolariciresinol* as colourless needles (110 mg), m.p. 59–60°. Further crystallization from chloroform-light petroleum (prisms) raised the melting point to 120–123° (Found: C, 67·4; H, 8·1; OMe, 35·1. $C_{22}H_{30}O_8$ requires: C, 67·8; H, 7·7; 4 OMe, 34·3%). The compound gave a negative ferric chloride reaction and the infra-red spectrum showed strong hydroxyl absorption at 3472 cm^{-1}.

Anhydro-di-O-methyl-seco-isolariciresinol (III, R = OCH_3). Methylation of seco-isolariciresinol (200 mg) with freshly dried potassium carbonate (500 mg) and dimethyl sulphate (1 ml) in boiling acetone (10 ml) for 20 hr gave a gum which crystallized from aqueous methanol as colourless prisms (98 mg), m.p. 120·5–121° (Found (avge. of two determinations): C, 70·75; H, 7·6; OMe, 33·1. $C_{28}H_{28}O_5$ requires: C, 70·9; H, 7·6; 4OMe, 33·3%). The compound gave a negative ferric chloride reaction and the infra-red spectrum showed no hydroxyl absorption. It did not depress the melting point of a sample, m.p. 119–120°, prepared from di-O-methyl-seco-isolariciresinol by dehydration with potassium hydrogen sulphate following the procedure of Schrecker and Hartwell[11] for the preparation of anhydro compounds.

3:4-*Bis*(3′:4′-*dimethoxybenzyl*)-*tetrahydrofuran* (III, R = OCH_3). (−)-Dimethylmatairesinol prepared in 71% yield from (−)-matairesinol by the method of Briggs *et al.*[2] was reduced to 2:3-bis (3′:4′-dimethoxybenzyl)-butan-1:4-diol by Haworth and Wilson's method[13] in 80% yield. The diol crystallised from aqueous methanol as prisms, m.p. 123–124° (lit.[11] m.p. 123–123·7°), undepressed by di-O-methyl-seco-isolariciresinol (identical infra-red spectrum). Dehydration of the diol

* Cf. the melting point recorded by K. Freudenberg and L. Knof,[10] for α-conidendrin.

with potassium hydrogen sulphate[11] and crystallisation of the product (80% yield) from methanol gave 3:4-bis(3′:4′-dimethoxybenzyl)-tetrahydrofuran as prisms, m.p. 119·5 (lit.[11] m.p. 118·4-119·7°), undepressed by anhydro-di-O-methyl-seco-isolariciresinol (identical infra-red spectrum).

Dibenzylmatairesinol (I, R = $C_6H_5CH_2$). (−)-Matairesinol (10 g) and potassium hydroxide (10 g) were heated under reflux with dry acetone (50 ml). Benzyl chloride (13 ml) was added and the mixture heated under reflux for 10 hr after which the solution was decanted from precipitated potassium chloride which was washed well with hot acetone. The combined solutions were concentrated and steam distilled to remove volatile impurities whereupon *dibenzylmatairesinol* was obtained in 95% yield. Four crystallizations from anhydrous ether containing a little dry benzene gave colourless prisms, m.p. 100°, insoluble in dilute alkali and giving a negative ferric chloride test (Found: C, 75·8; H, 6·7. $C_{32}H_{32}O_6$ requires: C, 75·8; H, 6·4%). The infra-red spectrum showed the absence of hydroxyl bands.

2:3-*Bis*(4′-*benzyloxy*-3′-*methoxybenzyl*)-*butan*-1:4-*diol* (II, R = $C_6H_5CH_2$). An ice-cooled solution of dry I (R = $C_6H_5CH_2$) (5 g) in sodium-dried ether (100 ml) was added with stirring over 2·5 hr to a suspension of lithium aluminium hydride (4 g) in dry ether (50 ml). After 3 hr stirring at room temp, excess lithium aluminium hydride was decomposed by addition of ethyl acetate (18 ml) and saturated ammonium chloride solution (17 ml). The precipitate was collected and extracted several times with boiling ethanol, the combined filtrates refiltered to remove precipitated ammonium chloride and the solvent removed *in vacuo*. Further inorganic salts were washed out with water. 2:3-*bis*(4′-*benzyloxy*-3′-*methoxybenzyl*)-*butan*-1:4-*diol* (62% yield) crystallized from methanol as colourless needles, m.p. 116–116·5°. (Found: C, 75·1: H, 6·7. $C_{34}H_{38}O_6$ requires: C, 75·25; H, 7·1%). Infra-red spectrum: 3268 (OH) cm^{-1}.

2:3-*Bis*(4′-*hydroxy*-3′-*methoxybenzyl*)-*butan*-1:4-*diol* (II, R = H). A mixture of II (R = $C_6H_5CH_2$) (0·5 g) and 10% palladium-charcoal (0·4 g) in methanol (25 ml) was shaken under pressure (2·5 atmos) with hydrogen for 4 hr. The catalyst was removed and the filtrate concentrated *in vacuo*. The resulting oil crystallized from dilute methanol to yield 2:3-bis(4′-hydroxy-3′-methoxybenzyl)-butan-1:4-diol (80% yield), m.p. 113·5°, undepressed by seco-isolariciresinol, $[\alpha]_D^{25}$ −36·7° (*c*, 1·16 in Me_2CO), identical infra-red spectrum (Found: C, 66·0; H, 7·0. Calc. for $C_{20}H_{26}O_6$: C, 66·3; H, 7·2%).

isoFlavones

Podospicatin. Podospicatin (11·9 g), m.p. and mixed m.p. 213·5–214°, was isolated by fractional crystallization of the light petroleum, benzene and ether extracts and from the sodium carbonate fractions of the benzene, ether and chloroform extracts. Circular R_f (A) 0·85, (B) 0·90.

Genistein. Genistein (5·1 g), m.p. and mixed m.p. 298–300° (decomp), was isolated by fractional crystallization of the ether extract after removal of quercetin. It was also isolated by fractional crystallization of the sodium carbonate fractions of the ether and chloroform extracts. Circular R_f (A) 0·75, (B) 0·90.

Flavonols

Quercetin. Quercetin (77·7 g), m.p. and mixed m.p. 313–316°, was isolated as the major product by fractional crystallization of the ether extract. It was also detected by paper chromatography in the sodium carbonate fractions of the ether, chloroform and ethyl acetate extracts. Circular R_f (A) 0·48 (B) 0·49.

Kaempferol. Paper chromatographic examination showed that quercetin was accompanied throughout by small amounts of a further yellow pigment, circular R_f (A) 0·58, (B) 0·74, separation of which was achieved by partition chromatography of quercetin mother liquors in 50–60% acetic acid on cellulose powder (Whatman, standard grade). Crystallization from 60% acetic acid and from aqueous ethanol gave kaempferol (200 mg), yellow needles, m.p. and mixed m.p. 280–283° (decomp) (Found: C, 63·2; H, 3·7· Calc. for $C_{15}H_{10}O_6$: C, 62·9; H, 3·5%) (identical infra-red spectrum). λ_{max} 266 mμ (log ε 4·24) and 370 mμ (log ε 4·40). Ultra-violet spectra in the presence of sodium acetate, sodium acetate–boric acid, sodium ethylate and sodium metaborate were identical with those for an authentic sample and also those recorded by Jurd *et al.*[10,11]

Flavononols

(+)-*Taxifolin*. After removal of matairesinol, the acidified aqueous phase of the sodium hydrogen carbonate fraction of the ether extract was extracted with ether and butan-1-ol. The concentrate from

the combined extracts was chromatographed in ethanol–chloroform–water (2 : 8 : 5) on columns of powdered cellulose following the procedure of Brewerton.[23] Crystallization of residues from slower moving fractions from aqueous ethanol gave (+)-taxifolin (180 mg), plates, m.p. and mixed m.p. 240° (decomp) $[\alpha]_D^{25}$ +48° (*c*, 1·0 in Me_2CO–H_2O) (Found: C, 57·8; H, 4·0. Calc. for $C_{15}H_{12}O_7 \cdot H_2O$: C, 57·5; H, 4·2%) (identical infra-red spectrum). λ_{max} 290 mμ (log ε 4·28) and shoulder at 330 mμ (log ε 3·56). Circular R_f (A) 0·77, (B) 0·69. The penta-acetate crystallized from absolute ethanol as needles, m.p. and mixed m.p. 118–120°. (Found: C, 58·1; H,4·45; Ac, 41·6. Calc. for $C_{25}H_{22}O_{12}$: C, 58·4; H, 4·3; 5 Ac, 41·8%).

(+)-*Aromadendrin*. Paper chromatography showed that taxifolin was accompanied by small amounts of a further 3-hydroxyflavanone (positive Pew's test[24]). The circular R_f values (A) 0·88, (B) 0·69 were identical with those of authentic aromadendrin and the ultra-violet spectrum determined by eluting the compound from paper strips by Geissman and Harbone's method[25] was identical with that of aromadendrin. λ_{max} 292 mμ and shoulder at 330 mμ. The compound was isolated in a crude condition by re-chromatography of the faster moving fractions from the partition columns above, in ethanol–chloroform–water (3 : 27 : 10). Acetylation and repeated purification from aqueous methanol gave (+)-aromadendrin tetra-acetate, m.p. 82–84° with shrinking at 60°, undepressed by a sample prepared from authentic (+)-aromadendrin (Found: C, 60·9; H, 4·4; Ac, 36·2. Calc. for $C_{23}H_{20}O_{10}$: C, 60·5; H, 4·4; 4 Ac, 37·7%).

Cyclitol

Sequoyitol. Extraction of the concentrate of the butan-1-ol extract with water, followed by concentration, gave a yellow syrup which on trituration with ethanol and long standing gave yields of optically inactive colourless leaflets. Recrystallization from aqueous methanol gave sequoyitol (840 mg), m.p. 240·5–241·5°, undepressed by an authentic sample (identical infra-red spectrum) (Found: C, 43·3; H, 6·9; OMe, 16·15. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3; 1 OMe, 16·0%). The penta-acetate, needles from benzene–ligroin, had m.p. 194° (lit.[26] m.p. 200°).

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CHEMISTRY OF THE PODOCARPACEAE—IV*

CONSTITUENTS OF THE HEARTWOOD OF *PODOCARPUS DACRYDIOIDES* A. RICH

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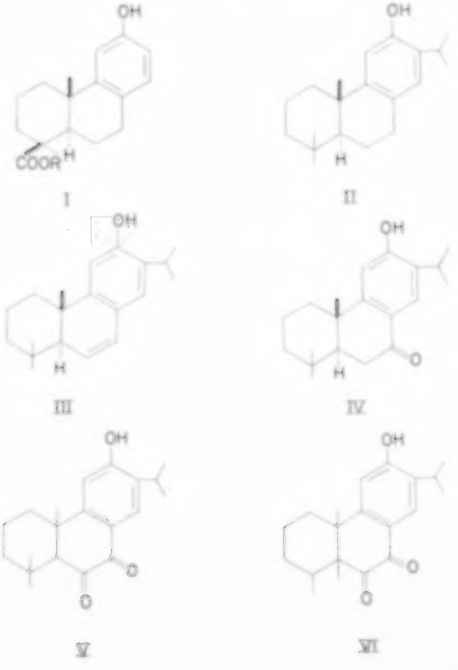
Abstract—The extractives of the heartwood of *Podocarpus dacrydioides* A. Rich. contain the known diterpenoid constituents, podocarpic acid (I, R = H), methyl podocarpate (I, R = CH_3), ferruginol (II), Δ^8-dehydro-ferruginol (III), sugiol (9-ketoferruginol, IV), xanthoperol (V) (in trace amount) and a new resin acid, $C_{20}H_{28}O_2$, for which the name pododacric acid is proposed. A saturated hydrocarbon also isolated is probably n-heptacosane.

Previous investigations of the constituents of *Podocarpus dacrydioides* A. Rich. (Maori name "kahikatea") have been limited to the essential oil which contains α-pinene,[1,2] β-pinene,[2] and cadinene[2] as the only identified products, and to the heartshake resin, which contains podocarpic acid (I, R = H).[3,4,5]



I II III IV V VI

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VOL. 7 1959

In a continuation of our studies of the constituents of the New Zealand species of the *Podocarpaceae* a systematic investigation of the constituents of the heartwood of *Podocarpus dacrydioides* has been carried out. Isolation of the constituents was facilitated by re-extraction of the concentrate from an initial methanolic extract mixed with Celite, with light petroleum, ether, ethyl acetate, water and methanol. The extraction scheme and the products identified from each extract are shown in Table 1.

Podocarpic acid (I, R=H) comprised the major constituent (0·37% yield) and was isolated with difficulty from the "acidic" and "phenolic" fractions of the ether extract. It also occurred largely as its magnesium salt in the water extract from which it could be isolated by acidification followed by chromatography.

By chromatography of the "neutral" fraction of the ether extract a phenolic compound, $C_{18}H_{24}O_3$, m.p. 211·5–212°, was isolated (0·02% yield) which, although insoluble in aqueous alkali and giving a negative ferric chloride reaction, readily dissolved in Claisen's cryptophenolic reagent[6] and gave an orange dye with diazotized *p*-nitroaniline. A comparison of the ultra-violet and infra-red spectra with those of podocarpic acid indicated that the compound was methyl podocarpate (I, R=CH_3) a fact confirmed by direct comparison with an authentic sample. Methyl podocarpate has not previously been isolated from natural sources.

Acetylation and re-chromatography of the "neutral" fraction of the ether extract after the separation of the bulk of methyl podocarpate led to the isolation of an acetate whose properties were identical with those of ferruginyl acetate isolated by Brandt and Thomas from *Dacrydium cupressinum*.[7] The identity was confirmed by de-acetylation to ferruginol (II) and characterization as the benzoate. Bredenberg,[8] when investigating the acetate obtained from *Juniperus communis* L.[9] has shown that ferruginyl acetate forms mixed crystals with its dehydroderivative (III) and also that ferruginol isolated from *Podocarpus ferrugineus*[10] and from *Dacrydium cupressinum*[7] contains small amounts of Δ^9-dehydroferruginol by a comparison of the ultra-violet spectra of the acetates with that of pure ferruginyl acetate. From a comparison of the spectra of our acetate and its hydrogenation product it would appear that it contained about 3 per cent of the dehydro derivative.

A phenolic ketone (0·01% yield) isolated from the "phenolic" fraction of the ether extract by chromatography was identified as sugiol (9-keto-ferruginol, IV)[11] by comparison with an authentic sample. Its occurrence together with ferruginol and Δ^9-dehydroferruginol is of interest in view of their co-occurrence in the related species *Dacrydium cupressinum*.[7,8] It has been shown that the C_9 methylene group of dehydroabietic acid and its derivatives undergo facile oxidation to the 9-oxo compounds[12,13] and that sugiol on reduction with aluminium isopropoxide undergoes simultaneous reduction and dehydration to the dehydroderivative.[8]

A small amount of a yellow crystalline compound eluted from the column after the above acetate possessed properties identical with those of xanthoperol, an artefact

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TABLE 1.—HEARTWOOD CONSTITUENTS OF *podocarpus dacrydioides*

HEARTWOOD
Extracted with methanol
Extract on Celite

(a) Light petroleum extract	(b) Ether extract			(c) Ethyl acetate extract	(d) Water extract (as salts)
(i) *crystallization*				(i) *$NaHCO_3$ solubles*	(i) *crystallization*
n-heptacosane sugiol (trace)	"Acidic" fraction	"Phenolic" fraction	"Neutral" fraction	pododacric acid	pododacric acid
	(i) *Benzene solubles*	(i) *crystallization*	(i) *chromatography*		(ii) *chromatography*
	podocarpic acid pododacric acid (trace) unidentified keto-acid	podocarpic acid	n-heptacosane methyl podocarpate ferruginol, Δ^8-dehydro-ferruginol, xanthoperol sugiol (trace)		podocarpic acid
	(ii) *Ether solubles*	(ii) *chromatography*			(iii) *paper chromatography*
	pododacric acid	sugiol podocarpic acid			unidentified phenols
	(iii) *Ethyl acetate solubles*				
	pododacric acid				

obtained along with sugiol from the wood of *Juniperus communis* L.[9] The original structure proposed for xanthoperol (V)[9] was subsequently changed[14] to VI mainly on the evidence of its failure to enolize spontaneously and the formation of a ketone different from sugiol on Clemmenson reduction. Wenkert and Chamberlin,[15] however, have recently pointed out that resistance to enolization of V would be caused by unfavourable non-bonded interaction between the equatorial C_1 methyl group and the C_{10} hydroxyl group of the enol form (phenanthrene numbering), while the failure to form sugiol on Clemmenson reduction implies that reduction, preceded by enolization, led to the more stable *cis* isomer of sugiol. The normal structure (V) can therefore be retained. The low yield of xanthoperol from *Podocarpus dacrydioides* and the failure to isolate further material in repeated attempts indicate that here too, it is an artefact.

VOL. 7 1959

The analysis of a crystalline hydrocarbon (0·004% yield) isolated from the light petroleum extract and by chromatography of the "neutral" fraction of the ether extract was in agreement with n-heptacosane, one of the more common hydrocarbons from heartwood species.

A keto-acid present in the "acidic" fraction of the ether extract in trace amount was separated from benzene solution by formation of its Girard derivative. All attempts to isolate the compound in a pure state as the oxime, semicarbazone or by chromatography of the crude 2:4-dinitrophenylhydrazone, however, have been unsuccessful.

Accompanying podocarpic acid in the ether extract was a small amount of a further resin acid, partial separation of which could be affected by the greater solubility of podocarpic acid in benzene. The less soluble acid (0·01% yield) could be isolated with difficulty by crystallization and from tarry residues by countercurrent distribution. It is a monocarboxylic acid, $C_{20}H_{28}O_5$, m.p. 213–214°, which can be characterized by the formation of a triacetate and a tribenzoate, thus accounting for all the oxygen functions. The presence of the carboxylic acid grouping and the hydroxyl groups can be confirmed by bands in the infra-red spectrum at 1701 cm^{-1} and at 3425 cm^{-1} and 3145 cm^{-1}, respectively. A positive ferric chloride reaction and the formation of a bright red dye with diazotized *p*-nitroaniline as well as aromatic bands at 1560 cm^{-1} and 1504 cm^{-1} in the infra-red spectrum shows that at least one of the hydroxyl groups is phenolic. With the assumption that only a single aromatic ring is present the formula leads to a tricyclic structure and it seems reasonable, therefore, to infer that this is a further diterpenoid acid of the podocarpic acid type. Such an acid possessing three hydroxyl groups has not been previously reported from natural sources and we propose the name pododacric acid. Further work on its structure is in progress.

EXPERIMENTAL

Analyses were by Dr. A. D. Campbell and associates, University of Otago, New Zealand. Infra-red spectra were measured as KBr disks with a Beckmann IR2 instrument (NaCl prism) and ultra-violet spectra for EtOH solutions with a Beckmann DU instrument. Light petroleum was of b.p. 50–60°.

Circular paper chromatography of resin acids was carried out on a Whatman No. 1 paper with the following solvent systems: (A) 25% aqueous acetic acid, (B) butan-1-ol–ammonium hydroxide–water (20 : 3 : 10). The position of spots was shown by spraying (a) successively with 5% aqueous

[14] J. B. Bredenberg, *Acta Chem. Scand.* **11**, 927 (1957).
[15] E. Wenkert and J. W. Chamberlin, *J. Amer. Chem. Soc.* **81**, 688 (1959).

sodium hydroxide, 1% alcoholic diazotized *p*-nitroaniline and 10% aqueous hydrochloric acid or with (b) a mixture of 1% ferric chloride and 1% potassium ferricyanide. Podocarpic acid has R_f (A) 0·7, (B) 0·8 and pododacric acid R_f (A) 0·8, (B) 0·7, the spots being coloured orange and red respectively, using spray reagent (a).

Extraction of Podocarpus dacrydioides *heartwood*. Continuous extraction (Soxhlet) of the finely ground wood (7·6 kg) with methanol for 25 hr and removal of the solvent gave a brown tar (670 g). The friable solid obtained after mixing with Celite and drying was successively re-extracted (Soxhlet) with (a) light petroleum, (b) ether, (c) ethyl acetate, (d) water and (e) methanol and the solvent removed from each extract. The residue from the ether extract (428 g) was redissolved in ether and fractionated in batches between saturated sodium hydrogen carbonate and 3% sodium hydroxide solutions. It was found necessary to use a large volume of sodium hydrogen carbonate solution to effect reasonable fractionation. Small quantities of resin acids were being extracted after use of 5 l. and extraction was still incomplete after 9 l. Little material was obtained by further trial extraction with 10% aqueous sodium carbonate solution. Acidification of the alkaline extracts gave an "acidic" fraction (169 g) and a "phenolic" fraction (154 g) as brown tars and a "neutral" fraction (58 g) remained as an oil. Similar fractions were obtained by treating the residue (26 g) from the ethyl acetate extract in the same manner. No identified products were obtained from the "phenolic" and "neutral" fractions of the ethyl acetate extract or from the methanol extract.

n-Heptacosane. On long standing the residue (2·6 g) from the light petroleum extract (a) gave a gum which contained crystalline material, separation of which was effected by trituration with acetone. After mechanical separation of a trace of sugiol (*vide infra*), the major solid was purified by washing with conc H_2SO_4 followed by water and crystallized from methanol–acetone to yield small glistening plates of n-heptacosane (50 mg), m.p. 59–60°. Further hydrocarbon (260 mg), m.p. 58·5° was obtained by chromatography of the "neutral" fraction of the ether extract (b) (*vide infra*). (Found: C, 85·3; H, 14·6; M (Rast), 392. Calc. for $C_{27}H_{56}$: C, 85·2; H, 14·8%; M, 381). The purified hydrocarbon gave negative tests for unsaturation and possessed an infra-red spectrum typical of saturated hydrocarbons.

Podocarpic acid (I, R = H). Podocarpic acid was expected to be present in the "acidic" fraction of the ether extract (b) in significant proportions. However, although it could be crystallized directly from the resin of the tree it could not be readily separated from the resins present in the "acidic" fraction. Trial attempts to effect separation by fractional crystallization of various amine salts by Harris and Sanderson's method[16] were unsuccessful. Partial separation (as shown by paper chromatography) was achieved by extraction of the dried residue with benzene followed by ether, leaving a residue soluble in ethyl acetate. Podocarpic acid was concentrated in the benzene solution but was contaminated by a keto-acid and a further acid, subsequently identified as pododacric acid. The ether solution contained a mixture of podocarpic and pododacric acids while pododacric acid was concentrated in the ethyl acetate solution. After extraction with 30% aqueous methanol which removed pododacric acid and separation of the keto-acid by formation of the water-soluble Girard derivative, podocarpic acid (1·8 g) slowly crystallized from the benzene solution on addition of light petroleum.

Podocarpic acid (17·7 g) was also isolated from the "phenolic" fraction of the ether extract (b) by repeated solution in ethyl acetate and precipitation with light petroleum, followed by slow crystallization from aqueous acetic acid.

On standing, the water extract (d) deposited a small amount of an acid magnesium salt, decomposition of which with hydrochloric acid, followed by extraction with ethyl acetate, gave a trace of pododacric acid. Acidification of the aqueous filtrate precipitated the bulk of the organic material, paper chromatography of which showed the presence of podocarpic acid and pododacric acid (trace) and unidentified phenolic compounds. Podocarpic acid was finally isolated by chromatography of a portion of the precipitated solid (450 mg from 4 g) on alumina (Brockmann III) from fractions eluted with methanol.

Podocarpic acid crystallized from 80% ethanol, or 60% acetic acid as long needles, m.p. and mixed m.p. 193–194°, $[\alpha]_D^{25}$ +139° (*c*, 2·2 in $CHCl_3$), λ_{max} 225 mμ (log ε 3·60) and 282 mμ (log ε 3·4). Methyl podocarpate, prepared by the use of an ethereal solution of diazomethane, had m.p. and mixed m.p. 211°. Methyl-O-methyl podocarpate, m.p. and mixed m.p. 128·5°, was prepared from podocarpic

[16] G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.* **70**, 339, 2079 (1948).

VOL. 7 1959

acid by treatment with dimethyl sulphate and anhydrous potassium carbonate in boiling acetone or from methylpodocarpate in methanolic solution by further treatment with diazomethane.

Pododacric acid. The ether extract of the "acidic" fraction from (b) above, on standing with benzene for 2 months with frequent trituration, deposited crystals mixed with tar. Dilution with an equal volume of methyl isobutyl ketone followed by rapid filtration gave crude pododacric acid (600 mg). Paper chromatography showed that the tar contained a mixture of podocarpic and pododacric acids, separation of which was achieved by countercurrent distribution in the system, light petroleum–n-butyl acetate–methanol–water (4 : 6 : 4 : 2). Twenty-three transfers concentrated pododacric acid in tubes 6–15 while podocarpic acid was concentrated in tubes 18–21 (paper chromatographic determination). Twelve further transfers with double withdrawal and removal of solvent gave crude pododacric acid (300 mg) from tubes 6–25.

Further crude pododacric acid (210 mg) was isolated from the ethyl acetate soluble residue of the "acidic" fraction from (b) and from the "acidic" fraction of the ethyl acetate extract (c) by slow crystallization from 30% methanol. Pure pododacric acid crystallized from 30% acetic acid or 30% methanol as colourless needles,* m.p. 213–214°, $[\alpha]_D^{25}$ +118° [*c*, 0·9 in $CHCl_3$–MeOH (5 : 1)] (Found: C, 68·8; H, 8·0. $C_{20}H_{28}O_5$ requires: C, 68·9; H, 8·1%). λ_{max} 225 mμ (log ε 3·74) and 284 mμ (log ε 3·4).

Tri-O-acetyl pododacric acid. Acetylation of pododacric acid with acetic anhydride–pyridine (100°; 3 hr) and isolation of the product by pouring onto crushed ice gave the *triacetate*, which crystallized from 80% methanol as granules, m.p. 160–160·5°, $[\alpha]_D^{22}$ +82° (*c*, 0·64 in EtOH) (Found: C, 66·3; H, 7·1; Ac, 26·6. $C_{26}H_{34}O_8$ requires: C, 65·8; H, 7·2; 3 Ac, 27·2%).

Tri-O-benzoyl pododacric acid. Benzoylation of pododacric acid with benzoyl chloride–pyridine (100°; 1 hr) and isolation of the product in the above manner gave the *tribenzoate*, needles (from ethanol), m.p. 135–136°, $[\alpha]_D^{22}$ +47° (*c*, 0·4 in EtOH) (Found: C, 75·3; H, 6·2; Bz. 44·8. $C_{41}H_{40}O_8$ requires: C, 74·5; H, 6·1; 3 Bz, 47·7%).

Sugiol (IV). Portions (35 g) of the "phenolic" fraction of the ether extract (b) were repeatedly chromatographed in benzene–ether (5 : 2) on activated magnesia, the initial fractions eluted with the same solvent and re-chromatographed on alumina (Brockman III). Fractions eluted with benzene–ether (3 : 1) gave sugiol (total yield 630 mg) on standing with benzene–light petroleum. Further elution of the columns with ether gave podocarpic acid (8·16 g). Sugiol was also isolated in trace amount from the light petroleum extract (a) and by chromatography of the "neutral" fraction of the ether extract (b). After repeated crystallization from acetic acid it was obtained as long colourless rods, m.p. and mixed m.p. 292·5–293°, $[\alpha]_D^{25}$ +36° [*c*, 0·4 in $CHCl_3$-pyridine (5 : 1)] (Found: C, 79·7; H, 9·1. Calc. for $C_{20}H_{28}O_2$: C, 80·0; H, 9·4%). λ_{max} 233 mμ (log ε 4·22) and 288 mμ (log ε 4·15) (identical infra-red spectrum). The acetate, prepared by the use of acetic anhydride–pyridine (100°; 2 hr) formed needles, m.p. 163–164°, from aqueous methanol (lit[17] m.p. 164–165°) (Found: C, 76·9; H, 8·6. Calc. for $C_{22}H_{30}O_3$: C, 77·15; H, 8·8%).

Methyl podocarpate (I, R = CH_3). The "neutral" fraction of the ether extract (b) was chromatographed in benzene on alumina (Brockman II). Initial fractions eluted with benzene gave n-heptacosane. Repeated rechromatography of fractions eluted with benzene–ether mixtures on alumina (Brockmann IV) gave crystalline material (1·34 g), m.p. 200°. Repeated crystallization from methanol gave methyl podocarpate as needles, m.p. and mixed m.p. 211·5–212° (Found: C, 75·2; 75·0; H, 7·9, 8·0. Calc. for $C_{21}H_{34}O_2$: C, 75·0; H, 8·4%). λ_{max} 222 mμ (log ε 3·74) and 282 mμ (log ε 3·41) (identical infra-red spectrum). The methyl ether, prepared by the use of dimethylsulphate and anhydrous potassium carbonate in boiling acetone, formed prisms, m.p. 128·5–129°, undepressed by methyl-O-methyl podocarpate (Found: C, 75·5, 75·5; H, 8·75, 8·5. Calc. for $C_{19}H_{26}O_2$: C, 75·5, H, 8·7%). λ_{max} 221 mμ (log ε 3·77) and 280 mμ (log ε 3·29) (identical infra-red spectrum).

Methyl-O-acetyl podocarpate. Acetylation of methyl podocarpate (43 mg) with acetic anhydride–pyridine (100°; 2 hr) and isolation of the product by pouring onto crushed ice gave methyl-O-acetyl podocarpate (50 mg), which crystallized from 50% methanol as needles, m.p. 122–123·5° (lit[18] m.p. 125–125·5°).

Ferruginol (II) *and* Δ^9*-dehydroferruginol* (III). The recombined fractions from the columns after separation of methyl podocarpate were acetylated and chromatographed in light petroleum on

* Traces of impurity inhibit crystallization giving oils on standing.

[17] P. Sengupta, S. Choudbury and H. Khastgir, *Chem. & Ind.* 861 (1958).
[18] E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.* **80**, 217 (1958).

alumina (Brockmann II). Fractions eluted with light petroleum slowly yielded a crystalline acetate, which on repeated crystallization from ethanol gave mixed crystals of ferruginyl and Δ^9-dehydroferruginyl acetates (120 mg), m.p. 80–81°, $[\alpha]_D^{22}$ +53° (*c*, 1·4 in $CHCl_3$) (Found: C, 80·8; H, 9·7. Calc. for $C_{22}H_{32}O_2$: C, 80·4; H, 9·8%). λ_{max} 269 mμ (log ε 3·14) and 277 mμ (log ε 3·18). The infra-red spectrum was identical with that of a sample of the acetate of ferruginol from *Dacrydium cupressinum*.[7] The infra-red and ultra-violet spectra of fractions eluted from the column with benzene–light petroleum (3 : 10) indicated that further acetate was present but the greater part could not be crystallized even on seeding. The brown oil obtained, had $[\alpha]_D^{22}$ +50° (*c*, 1·0 in EtOH), λ_{max} 272 mμ (log ε 3·17). Catalytic hydrogenation of the crystalline acetate with a palladium–charcoal catalyst gave pure ferruginyl acetate, which crystallized from ethanol as rods, m.p. 81–82°, $[\alpha]_D^{22}$ +60·5° (*c*, 0·9 in EtOH), λ_{max} 269 mμ (log ε 3·08) and 278 mμ (log ε 3·12).

Deacetylation of the crystalline acetate (100 mg) with 5% methanolic potassium hydroxide solution for 1 hr gave ferruginol as a pale yellow resin (80 mg), b.p. 140–145° (bath temp)/0·5 mm. Benzoylation of the resin (70 mg) with benzoyl chloride–pyridine (100°; 1 hr) and crystallization of the product from ethanol gave ferruginyl benzoate (40 mg) as rods, m.p. and mixed m.p. 154–155°.

Xanthoperol (V). After elution of the acetate from the column above, a fraction eluted with benzene gave yellow needles (2 mg), m.p. 250–260° (decomp). The infra-red spectrum and the properties of the compound were identical with those reported by Bredenberg and Gripenberg[8] for xanthoperol. Attempts to isolate further material were unsuccessful. Fractions eluted from the column with benzene–ether gave a mixture (29 mg) of sugiol and methyl podocarpate.

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VOL. 7 1959

POLYMORPHISM IN SUBSTITUTED BARBITURIC ACIDS

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Abstract—Of twenty substituted barbituric and thiobarbituric acids studied, nine have been found to exist in polymorphic forms. These are barbital, butethal, amobarbital, pentobarbital, thiopental, phenobarbital, aprobarbital, nostal and kemithal. The different modifications have been studied by X-ray diffraction and infra-red spectrophotometry, and the transition temperature ranges have been determined. The forms found are divided into two groups on the basis of their infra-red spectra. The tautomeric form of the compounds in the solid state is discussed briefly.

INTRODUCTION

POLYMORPHISM in substituted barbituric acids has been previously reported by a number of workers[1-5] in greater or less detail. This paper embodies the results of investigations of twenty such compounds, all commonly used in pharmaceutical preparations. All the acids are 5,5 disubstituted with a variety of alkyl and aryl substituents, two are N-methyl derivatives, and three are 2-thiobarbituric acids.

The trivial names used here are those adopted by *Chemical Abstracts*, and have been tabulated with synonyms and chemical names by Williams.[6]

EXPERIMENTAL

The techniques used for preparation of polymorphic forms were fusion, and crystallization of the supercooled melt, (if one formed) at different temperatures, precipitation from aqueous alkaline solution by acidification, crystallization from diethyl ether, and from aqueous alcohol, and evaporation of solutions in carbon tetrachloride, and chloroform, by blowing a jet of air over the solution to give rapid crystallization at low temperatures. All products were characterized by their X-ray diffraction patterns. Thermally unstable or metastable modifications were heated for an hour at 40°, 50°, etc. up to fusion, and examined after each step.

X-ray patterns were obtained on a Norelco wide range Geiger Diffractometer, using nickel filtered copper radiation (1·5418 Å). Infra-red spectra were obtained on a Perkin–Elmer Model 21 double-beam spectrophotometer. The samples were prepared as paraffin mulls and hexachlorobutadiene mulls, confined between two rocksalt plates. Sodium chloride optics were used. The infra-red spectra of different modifications in chloroform solution all at the same concentration, were also obtained.

The reversibility of the thermal transformation of one form to another was investigated by slowly cooling the more stable form through the transformation temperature range, and in some cases by cooling it to liquid air temperatures. The product was then examined for traces of the less stable form.

RESULTS

Of the twenty barbituric acids studied, nine were found to be polymorphic. These compounds are listed in Table 1, together with the methods of preparation of the different forms. The other

[1] R. Fischer, *Ber. Dtsch. Pharm. Ges.* **270**, 149 (1932).
[2] R. Fischer and A. Kofler, *Ber. Dtsch. Pharm. Ges.* **270**, 207, (1932).
[3] Maria Brandstatter, *Z. Phys. Chem.* **A191**, 227 (1942).
[4] T-Y. Huang, *Acta Pharm. Intern.* **2**, 43, (1951).
[5] T-Y. Huang, *Acta Pharm. Intern.* **2**, 95 (1951).
[6] P. P. Williams, *Analyt. Chem.* **31**, 140 (1959).

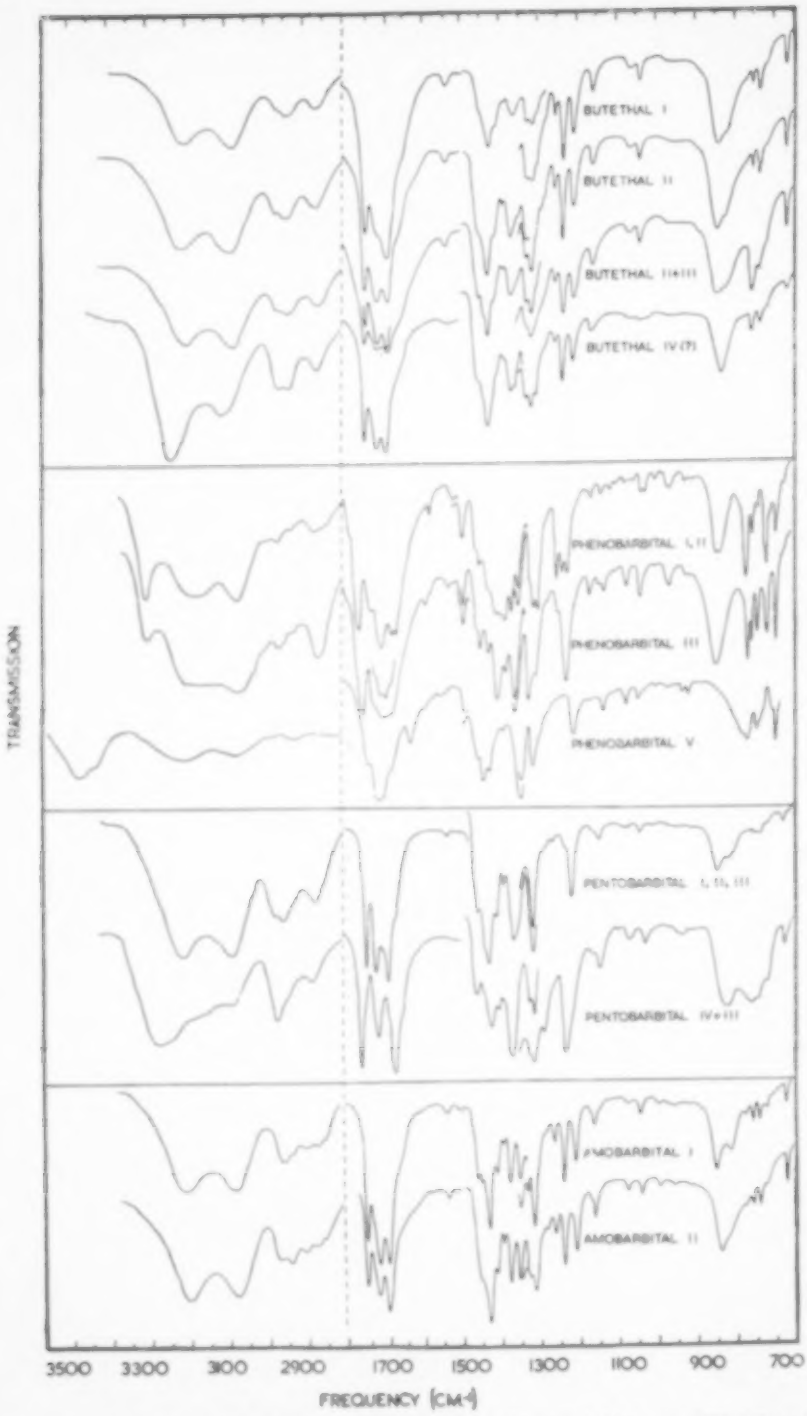

FIG. 1. Infra-red spectra of polymorphic barbituric acids, recorded between 4000–650 cm^{-1}. Hexachlorobutadiene used as a mulling liquid in regions of paraffin oil absorption. A break in the curve indicates a change in sample concentration or of mulling liquid.

VOL. 7 1959

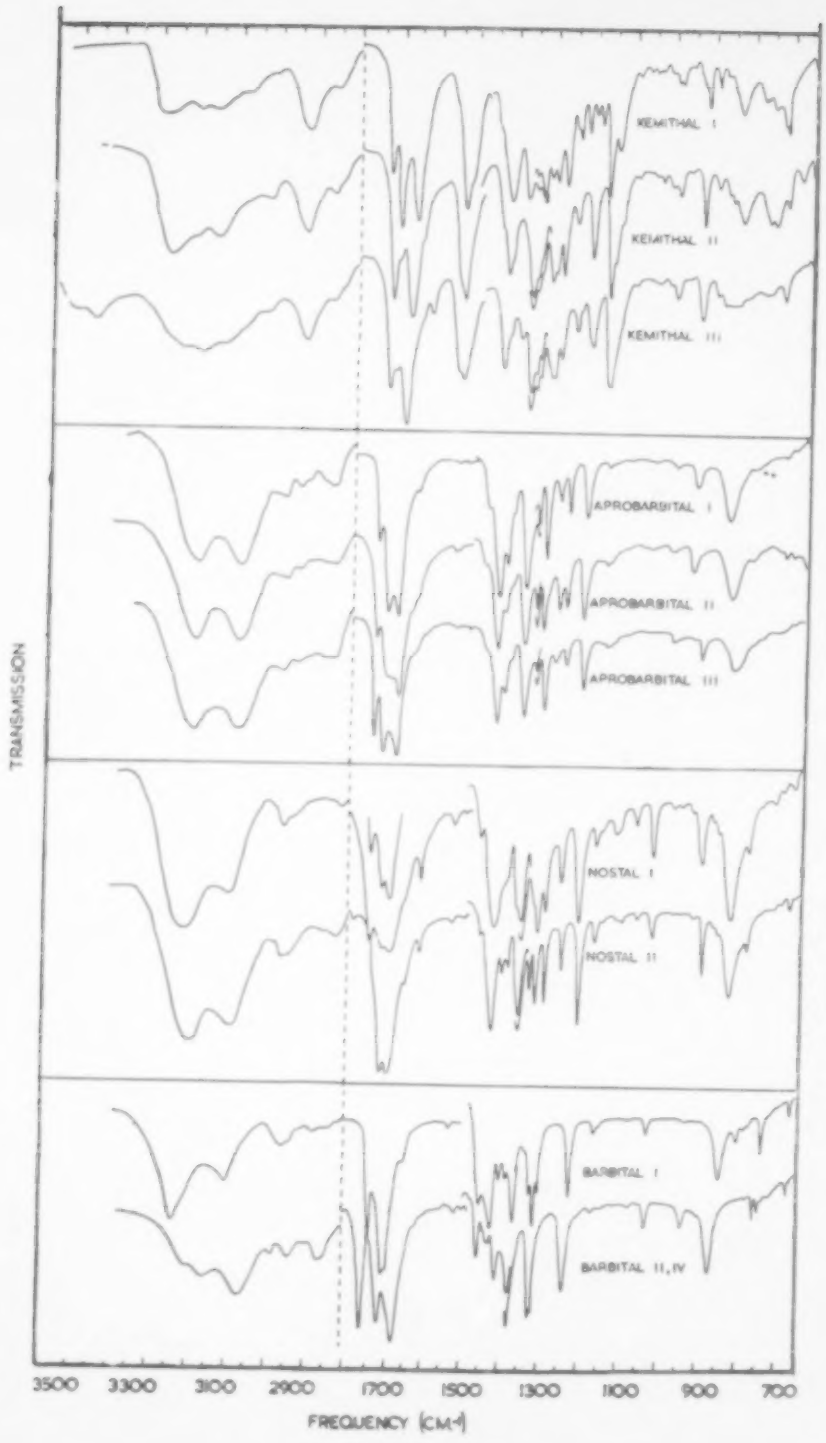

FIG. 1. (*cont.*)

TABLE 1

Compound	Room temp	40°	50°	60°	70°	80°	90°	100°	110°	120°	130°	140°	150°	160°	170°	180°
Barbital	IV[a]	IV	IV	IV	IV (+ II)	IV + II	IV + II	II	II	II	II	II + I	I	I	I	I
Butethal	III + II[b] II[c]	III + II II	III + II II	III + II + I II + I	I I	I I	I I	I I	I I	I I						
Amobarbital	II[d]	II	II	II	II	II	II	II	II	II	II + I	I	I			
Pentobarbital	IV + I[e] III[c] II[g]	IV + I III II	IV + I III II	IV + I III II	IV + I III + II + I II	(IV +) I II + I II + I	I II + I II + I	I II + I II + I	I II + I II + I	I I I						
Thiopental	II[g]	II	II	II	II	I	I	I	I	I	I	I				
Phenobarbital	V[a]	V + III	V + III	III	III	III	III	III	III	III	II + I	II + I	II + I	I	I	
Aprobarbital	III[h]	III	III + II	III + II	II	II	II	II + I	II + I	II + I	I					
Nostal	II[d] I[h]	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	II I	
Kemithal	III[a]	III	III	III	III + II	II	II	II	II + I	I	I					

[a] Precipitated from alk. soln. by acidn.
[b] cryst. from chloroform
[c] crystn. of supercooled melt at room temp.
[d] cryst. from diethyl ether
[e] fused
[f] cryst. from chloroform under air jet
[g] cryst. from carbon tetrachloride under air jet

VOL. 7 1959

eleven, butabarbital, cyclobarbital, cyclopal, dial, hexobarbital, mephobarbital, probarbital, rutonal, sandoptal, secobarbital and thiamylal did not give polymorphic forms with the methods used. X-ray patterns not previously published are presented in Table 2, and the distinct infra-red patterns in Fig. 1. Table 1 shows the results of heating a less stable modification for an hour at a time to regularly increasing temperatures, and cooling to room temperature for X-ray examination between steps. Where two modifications co-exist over a range of temperatures, the proportion of the more stable one increases with rising temperature.

All the thermal transformations were irreversible under the experimental conditions used. However, since all examinations were carried out at room temperature, the actual behaviour at higher temperatures is not necessarily known.

The infra-red spectra of different forms of a compound in chloroform solution were always identical, showing that the various crystallization techniques did not result in decomposition.

Details of the modifications studied are as follows:

Barbital (*5,5-diethyl barbituric acid*). Huang[5] has published X-ray patterns for four forms, only three of which (I, II and IV) were prepared in this work. Forms II and IV have similar X-ray patterns, and identical infra-red spectra. Form I is quite different from these, both in its X-ray pattern, and over the whole range of the infra-red spectrum. Grinding form II results in its transformation to form I.

Butethal (*5-ethyl-5-n-butyl barbituric acid*). Four forms have been prepared. X-ray patterns of forms I[6] and II[7] have already been published, but redetermination of that of form II showed discrepancies from Huang and Jerslev's data, and the revised pattern appears in Table 2. Modification IV was formed in small quantities with form II by rapid evaporation of a carbon tetrachloride solution with a jet of air. It has not been studied in detail, but its X-ray pattern is characterized by lines at 9·05 (m), 7·83 (mw), 6·42 (mw), 5·63 (w), 4·35 (s), 3·85 (mw) and 2·98 Å (m). The X-ray patterns of forms I and II are similar, and the infra-red patterns show only slight differences in the C—O stretching and C—H bending regions. Form III was prepared only in association with form II, and some lines ascribed to form II are present in the X-ray pattern in Table 2. This pattern is quite different from those of I and II, and the infra-red spectrum of III differs from those of I and II in the region 900–700 cm^{-1}. Grinding a mixture of forms II and III resulted in a form giving an infra-red spectrum different from the others, particularly in the N—H stretching region. This may be due to form IV, but X-ray verification of this was impracticable. Form I is transformed to form II very easily by grinding.

Amobarbital (*5-ethyl-5-isoamyl barbituric acid*). Two forms have been found. The X-ray pattern of form I (which can be prepared by crystallisation from chloroform) has been published,[6] and differs markedly from that of form II. The differences in the infra-red patterns are small, being intensity differences in the C—O stretching and C—H stretching and bending regions, and some peak shifts in the region 900–700 cm^{-1}.

Pentobarbital (*5-ethyl-5-(1-methyl butyl) barbituric acid*). Brandstatter[3] has reported the existence of two forms. The X-ray pattern of form II is closely similar to that published by Huang and Jerslev,[7] but this pattern is given in Table 2, to emphasize its similarity to that of form III. The differences between these patterns are the splitting of certain peaks in form II to produce doublets in III. This suggests that one modification may be a disordered form of the other. The X-ray pattern of I is similar in many respects to both these. These similarities are reflected in the identity of the infra-red spectra of all these three forms. Pentobarbital IV was invariably contaminated to a certain extent by form I, but as the X-ray patterns of both are fairly simple, that of form IV can be reported with some certainty. It is possible that weak reflections from IV occur at the same positions of strong ones from I. The infra-red spectrum of IV differs from that of the other forms over the whole spectrum. The infra-red and X-ray patterns of pentobarbital II and III bear a strong resemblance to those of amobarbital I, suggesting that these are structurally similar. The thermal transition of form III to form I outlined in Table 1 probably involves form II, but the similarity between II and III makes this difficult to determine with certainty.

Thiopental (*5-ethyl-5-(1-methyl butyl)-2-thiobarbituric acid*). Two forms have been found. The X-ray pattern of form I has been published[6] and is somewhat similar to that of form II. The infra-red spectra of the two are identical.

[7] T-Y. Huang and B. Jerslev, *Acta Pharmacol et Toxicol.* **7**, 227 (1951).

TABLE 2

Amobarbital I		Aprobarbital IV		Butethal II	
d	I/I_1	*d*	I/I_1	*d*	I/I_1
11·25	90	9·1	100	10·7	54
9·90	100	5·91	26	9·75	100
8·95	14	5·21	10	7·25	37
7·9	2	5·04	8	6·93	77
7·45	2	4·54	15	5·98	8
6·98	69	4·09	5	5·37	66
6·24	4	3·66	19	5·14	9
5·96	30	3·37	33	4·99	5
5·52	96	3·03	100	4·85	29
5·37	19	2·88	5	4·47	18
4·98	19			4·33	6
4·87	30			4·07	4
4·78	26			3·99	39
4·54	12			3·93	3
4·46	23			3·74	6
4·38	2			3·67	2
4·19	44			3·60	25
3·76	73			3·45	4
3·68	16			3·31	8
3·63	21			3·18	13
3·56	4			3·09	6
3·50	12			2·95	5
3·27	11			2·91	4
3·20	2			2·81	2
3·17	5			2·680	6
3·10	45			2·570	7
3·05	14			2·490	3
3·00	6				
2·94	3				
2·88	2				
2·827	20				
2·760	3				
2·735	6				
2·686	8				
2·555	8				
2·540	9				
2·508	2				
2·450	4				
2·424	5				
2·344	3				
2·298	2				
2·191	2				
2·005	2				
1·985	4				
1·883	3				

VOL. 7 1959

TABLE 2 (*cont.*)

Butethal III		Kemithal I		Kemithal II	
d	I/I_1	*d*	I/I_1	*d*	I/I_1
20·2	21	15·2	30	13·0	76
11·5	81	12·5	20	6·93	100
10·6	11 (II)	8·75	5	6·70	49
10·15	100	8·45	5	6·49	15
9·85	23 (II)	7·97	25	6·24	5
9·30	38	7·70	25	6·07	5
8·88	6	7·53	10	5·79	27
8·28	5	6·51	10	5·45	84
7·50	5	6·28	20	5·25	5
7·28	5 (II)	6·15	10	5·08	36
7·12	23	6·07	10	4·96	3
6·90	27 (II)	5·91	10	4·67	24
6·62	21	5·80	20	4·55	14
6·38	39	5·68	35	4·41	5
5·34	90	5·54	10	4·33	9
5·08	29	5·23	100	4·22	14
4·86	18	5·01	10	4·09	12
4·74	15	4·93	10	4·05	30
4·43	20	4·75	5	3·91	15
4·18	27	4·67	10	3·82	41
4·06	30	4·57	15	3·69	9
3·99	36	4·54	15	3·63	7
3·95	9	4·41	10	3·52	48
3·82	86	4·32	10	3·42	63
3·67	18	4·13	20	3·34	7
3·50	26	4·04	10	3·27	31
3·45	9	3·96	10	3·11	19
3·40	8	3·83	20	3·07	9
3·31	11	3·77	5	2·97	24
3·26	5	3·72	10	2·92	7
3·23	5	3·66	20	2·875	7
3·17	6	3·53	20	2·815	10
3·10	9	3·49	20	2·785	9
3·00	20	3·42	20	2·633	5
2·96	23	3·39	15	2·533	10
2·91	15	3·32	10	2·500	5
2·875	5	3·21	30	2·462	10
2·806	5	3·13	20	2·355	3
2·747	3	2·825	15	2·338	3
2·565	5	2·706	5	2·302	7
		2·501	10	2·020	5
				1·993	3

TABLE 2 (*cont.*)

Nostal I		Pentobarbital I		Pentobarbital II	
d	I/I_1	*d*	I/I_1	*d*	I/I_1
11·9	62	11·25	100	11·05	100
7·52	8	7·94	20	10·05	25
6·45	65	7·35	16	8·9	17
6·28	18	7·02	81	7·04	87
5·95	94	6·71	2	6·46	8
4·74	62	6·15	2	5·60	72
4·68	24	5·53	61	5·48	87
4·61	8	5·11	3	5·04	6
4·48	10	4·99	9	4·84	57
3·96	33	4·83	34	4·66	6
3·88	10	4·48	11	4·51	17
3·81	22	4·21	3	4·26	6
3·62	27	4·15	2	3·82	6
3·56	41	4·02	7	3·67	36
3·43	24	3·96	2	3·30	4
3·29	14	3·76	36	3·25	4
3·23	33	3·71	7	3·15	8
3·20	9	3·66	3	3·04	21
3·14	100	3·57	18	2·817	19
3·09	4	3·51	16	2·747	4
2·99	39	3·42	3	2·563	9
2·92	8	3·38	2	2·548	6
2·734	8	3·23	2		
2·694	19	3·18	7		
2·502	12	3·14	4		
2·301	12	3·03	16		
2·238	12	2·92	2		
2·174	5	2·865	4		
1·949	5	2·822	18		
1·908	4	2·732	7		
		2·550	11		
		2·483	3		
		2·408	2		
		2·325	2		
		2·294	2		
		2·109	3		
		1·992	3		

VOL. 7 1959

TABLE 2 (*cont.*)

Pentobarbital III		Pentobarbital IV		Phenobarbital V	
d	I/I_1	*d*	I/I_1	*d*	I/I_1
11·2	45	13·8	88	15·4	100
10·85	100	6·21	100	12·3	2
10·1	55	6·07	40	8·94	2
9·9	40	5·07	31	7·75	64
8·86	23	4·92	44	6·5	1
7·95	8	4·66	23	6·3	1
7·13	57	4·29	20	5·90	72
6·83	45	3·95	10	5·45	49
5·83	6	3·74	33	5·17	20
5·62	54	3·28	6	5·04	1
5·44	88	2·94	15	4·75	14
4·84	42	2·865	15	4·68	4
4·52	17	2·635	5	4·45	1
4·09	18	2·620	5	4·33	2
4·00	19			4·18	1
3·71	11			4·11	1
3·61	37			4·02	2
3·43	3			3·91	94
3·41	5			3·76	5
3·25	3			3·56	17
3·16	9			3·50	8
3·08	3			3·39	7
3·03	17			3·33	2
2·96	6			3·25	3
2·91	3			3·16	2
2·82	15			3·09	28
2·707	7			2·98	34
2·574	6			2·868	14
2·542	8			2·788	34
1·994	8			2·749	4
				2·690	10
				2·615	10
				2·588	7
				2·483	4
				2·423	1
				2·410	1
				2·367	3
				2·341	3
				2·331	3
				2·281	1
				2·225	7
				2·166	3
				2·147	2
				2·094	1
				2·080	1

TABLE 2 (*cont.*)

Pentobarbital III		Pentobarbital IV		Phenobarbital V	
d	I/I_1	*d*	I/I_1	*d*	I/I_1
				2·063	3
				2·015	3
				1·997	1
				1·983	2
				1·931	6
				1·865	2
				1·824	2
				1·719	2
				1·701	1
				1·675	1
				1·666	1
				1·643	1
				1·626	1
				1·606	1
				1·546	1

Thiopental II	
d	I/I_1
13·5	100
6·76	22
6·37	3
6·07	4
5·10	9
4·79	3
4·45	3
4·34	7
4·04	2
3·90	4
3·77	2
3·33	3
3·14	3

Phenobarbital (*5-ethyl-5-phenyl barbituric acid*). Six forms are now known. Huang[4] has reported X-ray patterns for forms I, II, III, IV and IVa, and the pattern of a new form, V, appears in Table 2. Forms IV and IVa were not prepared in this work. Forms I and II have similar X-ray patterns and identical infra-red spectra. Forms III and V are very different from these, and from each other, both in X-ray patterns and over the whole infra-red spectrum. Phenobarbital II is readily convertible to form III on grinding, and form V will slowly change to III, spontaneously.

Aprobarbital (*5-allyl-5-isopropyl barbituric acid*). Four forms have been reported: X-ray patterns of I, II and III have been reported by Huang,[5] and the preparation of IV by Williams.[6] Form IV is

[6] P. P. Williams, *Nature, Lond.* **179**, 1189 (1957).

most unstable, reverting to III when dry, and has not been studied in detail. The X-ray pattern of the wet crystals is given in Table 2. Forms I, II and III have quite different X-ray patterns and show differences in their infra-red spectra. The spectra of forms I and II differ in the relative intensities of peaks in the 1300–1200 cm^{-1} region, and that of III differs from these in the C—O stretching and C—H bending regions, and in the 900–850 cm^{-1} region.

Nostal (*5-isopropyl-5-(2-bromallyl) barbituric acid*). Two forms have been prepared. The pattern of II already reported[9] is quite different from that of I, and their infra-red spectra show differences in the C—O stretching and C—H bending regions. Both I and II are thermally stable, but form I readily changes to II on grinding.

Kemithal (*5-allyl-5-cyclohexenyl-2-thiobarbituric acid*). Three forms have been prepared. Forms I and II can be prepared only by heating III. The X-ray patterns of all three (that of form III has been previously published[9]) are quite distinct. The spectra of I and II differ only below 1800 cm^{-1}, whereas that of form III differs markedly from these in the N—H stretching region. Below 1800 cm^{-1}, II and III are similar, showing small differences in the C—O stretching and 900–650 cm^{-1} regions.

DISCUSSION

It has been observed in this work that major differences in the infra-red spectra of different modifications of the same compound are invariably accompanied by major differences in the X-ray pattern. Any similarity between the X-ray patterns is always reflected in a very close similarity or identity in the infra-red spectra.

No correlation is apparent between molecular structure, and the occurrence of polymorphism in these compounds. For example, phenobarbital occurs in six known modifications, and yet mephobarbital (N-methyl phenobarbital) is monomorphic. This suggests that the N-hydrogen atom is involved in intermolecular bonding in at least some of the forms of phenobarbital. However, the monomorphism of rutonal (5-methyl-5-phenyl barbituric acid) is more difficult to explain. The monomorphism of dial (5,5-diallyl barbituric acid) is rather surprising in view of the tetramorphism of barbital. Although Hertel[9] reports that dial and barbital II have very similar structures, attempts to form other barbital-like structures with dial, by seeding dial melts with different forms of barbital, and by forming mixed crystals, met with no success. On the other hand, despite the tetramorphism of aprobarbital, it would have been expected that the introduction of a bromine atom on the allyl group to form nostal would have stabilized the structure, and produced a monomorphic compound. The fact that the two forms of nostal are not interconvertible by heat alone is almost certainly due to the presence of the large bromine atom. The trimorphism of kemithal is also rather surprising in view of the large molecule and the availability of only two carbonyl groups for intermolecular bonding.

Comparison of the infra-red spectra of different forms of the same compound shows that large differences in the C—O stretching region are almost always accompanied by large differences in the C—H bending region. This suggests that such a change in the C—O region, caused by a major rearrangement of the molecules in the lattice, is accompanied possibly by changes in molecular symmetry, and by a redisposition of the C_5 substituents, thereby modifying the selection rules governing the appearance and intensity of peaks.

A large group of spectra are almost identical in the N—H stretching region—two almost equally intense peaks at about 3200 and 3080 cm^{-1}. The same two peaks characterize the solution spectra in chloroform at high concentration,[10] when the monomer N—H stretching peak at 3360 cm^{-1} is reduced in intensity, and they are also typical of the spectra of cyclic amides.[11] The carbonyl bands of this group of modifications usually consist of three simple peaks, and are again, rather like the carbonyl bands of the solution spectra.[10] The spectra concerned are those of nostal I and II, amobarbital I and II, aprobarbital I, II and III, pentobarbital I, II and III, and butethal I, II and III.

A strong, sharp band at around 840 cm^{-1} is associated with the spectra of solid barbiturates,[12] and a broad band in this region is observed in solution spectra.[10] This is undoubtedly the band of similar appearance, due mainly to the N—H out-of-plane bending vibration, observed at 700–750 cm^{-1} in monosubstituted amides and at 840 cm^{-1} in cyclic amides.[13] This band is similar in all the first group of modifications.

[9] E. Hertel, *Z. Phys. Chem.* Abt. B. 117 (1935).
[10] C. J. Umberger and Grace Adams, *Analyt. Chem.* **24**, 1309 (1952).
[11] S. E. Darmon and G. B. B. M. Sutherland, *Nature, Lond.* **164**, 440 (1949).
[12] L. Levi and C. E. Hubley, *Analyt. Chem.* **28**, 1591 (1956).
[13] T. Miyazawa, T. Shimanouchi and S. Mizushima, *J. Chem. Phys.* **24**, 408 (1956).

VOL. 7 1959

The remaining spectra (excluding those of thiobarbituric acids) are often greatly different from one another and from the first group in the N—H and C—O regions. Large differences in N—H spectra between modifications of the same compound are generally paralleled by large differences in the C—O region. This suggests that the N—H:C—O intermolecular interaction is important in these structures. Some of these spectra are very complex in the N—H and C—O regions, suggesting a complex system of intermolecular interactions, and it may be significant that there appears to be some degree of correlation between such complexity, and the occurrence of large spacings in the X-ray pattern.

Enolization could be a factor contributing to the polymorphism found, but the occurrence of N—H stretching and out-of-plane bending vibrations in the first group of spectra, at the characteristic frequencies of keto amides, and the absence of any absorption at a frequency high enough to be assigned to an O—H stretching vibration, indicates that these compounds exist in the solid and in chloroform solution as the keto forms.

Although the hydrogen stretching regions of the second group of spectra differ from those of the first group, it is only in phenobarbital V and kemithal III that peaks occur that are likely to arise from O—H stretching vibrations. It may be significant that it is only in the spectra of these two modifications that the N—H out-of-plane bending vibration appears to be anomalous. Unlike the other modifications of these compounds these two show a peak at around 1620 cm^{-1}. A similar peak in the spectrum of acetyl urethane led to the suggestion that this latter compound is completely enolized.[14] Although phenobarbital and kemithal contain unsaturated C_5 substituents, no absorption appears in this region of their other modifications.

It therefore seems probable that in phenobarbital V and kemithal III enolization has occurred, but the infra-red evidence favours the triketo configuration for all the other modifications.

[14] H. M. Randall, R. G. Fowler, N. Fuson and J. D. Dangl, *Infra-Red Determination of Organic Structures*. Van Nostrand, New York (1949).

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VOL.
7
1959

LOCATION OF A BRANCH IN A SATURATED CARBON CHAIN*

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Abstract—Oxidative degradation by chromic acid in glacial acetic acid has been developed as an effective method for location of a branch in a saturated carbon chain. Detection of cleavage products by use of gas phase chromatography allows convenient application of the method to samples of 3–10 mg. Several branched-chain acids and a branched-chain hydrocarbon have been found to yield the expected cleavage products; however, selective attack on a branch located *alpha*, *beta* or *gamma* to carboxyl is not significant. The mechanism of the oxidation and the protective influence of carboxyl are discussed.

ALTHOUGH there are available to the organic chemist numerous methods for stepwise degradation of a carbon chain *via* attack at a multiple linkage or a polar substituent group, in most instances the chain is degraded by only one or two carbon atoms per operation. In instances where a branch in a chain is located remotely from a polar functional group, stepwise degradation until the branch is reached becomes laborious and is likely to require relatively large amounts of starting material. Our attention has been directed to this problem as a result of our investigations of the branched-chain acids from tubercle bacillus, notably the physiologically active C_{27}-phthienoic acid.[1] Structural features near carboxyl and the adjacent double bond were elucidated[2] by investigation of rather small amounts of material, largely by utilization of analytical and physical measurements; however, subsequent investigations[3] have indicated only a strictly tentative structure for the branching group which is more remote from carboxyl than the 4-position.[4] Thus, degradative methods designed to directly attack the position of branching in an alkane chain have come under investigation.

Among the processes in which a tertiary position is selectively attacked under appropriate conditions are halogenation, nitration and sulfonation; however, these methods suffer the common disadvantage that additional steps are necessary in order to eventually break the chain and give products whose identification will reveal the structure of the substance degraded. In contrast, several methods of oxidation not

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† Recipient of a National Science Foundation Faculty Fellowship, 1958–1959.

[1] J. Cason and G. Sumrell, *J. Biol. Chem.* **192**, 405 (1951); H. Husseini and S. Elberg, *Amer. Rev. Tuberc.* **65**, 655 (1952).

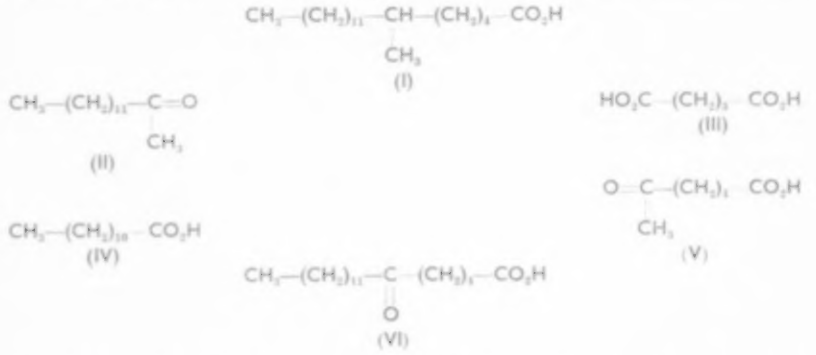
[2] J. Cason, N. K. Freeman and G. Sumrell, *J. Biol. Chem.* **192**, 415 (1951); J. Cason and C. F. Allen, *Ibid.* **205**, 449 (1953).

[3] J. Cason, H.-R. Urscheler and C. F. Allen, *J. Org. Chem.* **22**, 1284 (1957).

[4] Investigations carried out at the Oxford laboratories, based originally on degradation of a mixture of higher fatty acids from the tubercle bacillus, have resulted in assignment of the structure, 2,4,6-trimethyl-2-tetracosenoic acid, to a component acid termed mycolypenic acid [cf. D. J. Millin and N. Polgar, *J. Chem. Soc.* 1902 (1958) and references cited therein]; however, the complexity of the mixture of α,β-unsaturated acids in the tubercle bacillus is such that the identity of C_{27}-phthenoic acid and mycolypenic acid (cf. ref. 3) can hardly be regarded as established. Thus, degradation of C_{27}-phthienoic acid is being pursued actively, as is separation of other components from the mixture.

only attack a tertiary hydrogen rapidly but also cleave the chain. Although ozone has been reported[5] to react "primarily at the tertiary carbon atoms", in the present investigation the rate of reaction was found to be quite slow, and the yield of cleavage products was very small. Oxidation with alkaline permanganate or with sodium dichromate in acetic acid appeared insufficiently selective to be of interest; however, oxidation with chromic acid in acetic acid[6] has proved quite useful, and utilization of gas phase chromatography for detection of cleavage products renders the method effective for degradation of quantities of 5 mg or less.

In order to determine if the reaction conditions employed by Spielman[6] could be improved, the oxidation of 6-methyloctadecanoic acid (I) was examined. Expected primary cleavage products are those represented by formulas II–VI. In this oxidation, as well as others examined, the keto acid corresponding to VI was obtained in such small amount that it was rarely detected at all. This point is of interest in connection with the mechanism of the oxidation to be developed subsequently. For evaluation of the effectiveness of conditions, the yield of ketone II was determined. It is the



only neutral primary degradation product and appeared as the sole band in gas chromatography of the neutral product. The more pertinent results are summarized in Table 1. The conditions recommended by Spielman (similar to Run 1) were found to employ a favorable ratio of oxidizing agent, in that most of the starting acid was consumed (cf. footnote *b*) and increase in oxidizing agent lowered the yield of 2-tetradecanone (Run 2). Optimum conditions appear to involve dissolution of the reactants before heating and use of a rather dilute solution (Runs 3–5); therefore, the conditions represented by Run 5 have been adopted as those preferred for the degradation.

The expected cleavage products have also been obtained from 9-methyloctadecanoic acid and from 10-methyloctadecanoic acid (VII). From 2,5-dimethyloctadecanoic acid, there were obtained only the cleavage products resulting from the branch at the 5-position; therefore it is indicated that carboxyl stabilizes the adjacent position against oxidative attack. Further investigation of the stabilizing influence of carboxyl is discussed below. Representative recorder tracings obtained from gas chromatography of degradation products are illustrated in Fig. 1. The two lower curves are

[5] J. H. Durland and H. Adkins, *J. Amer. Chem. Soc.* **61**, 429 (1939).

[6] This method of oxidation was used on a relatively large scale by M. A. Spielman, *J. Biol. Chem.* **106**, 87 (1934), to establish the structure of tuberculostearic acid as 10-methyloctadecanoic acid. From 2 g of tuberculostearic acid were obtained 30 mg of the semicarbazone of 2-decanone and 30–70 mg of azelaic acid.

TABLE 1. OXIDATION OF 300 mg OF 6-METHYLOCTADECANOIC ACID

Temp: 60–70°. Time: 2–3 hr 6 moles of CrO_3 per mole of acid, unless otherwise indicated.

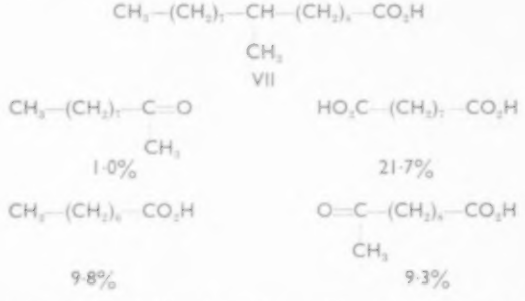
Run No.	Method of CrO_3 addition	ml of HOAc	Yield of	
			Neutral (mg)	2-Tetradecanone (mg)
1	solid to hot solution	7·5	12	4
2[a]	solid to hot solution	7·5	22	2·5
3	solution to hot solution	18	20	5
4	dissolved in cold solution	22	21	8·5
5[b]	dissolved in cold solution	50	24	9·5

[a]In this run, there were used 9 moles of CrO_3 per mole of acid.

[b]In this run, there were also detected 18 mg of dodecanoic acid and 30 mg of the starting acid (by gas chromatography of the esters).

characteristic ones, whereas the upper curve shows the largest secondary bands that have been encountered.

Weight per cent yields were rather carefully determined for the four principal degradation products of acid VII, and these values are recorded beneath the formulae for these compounds.



The total yield of keto acid and dibasic acid, resulting from the two dominant cleavages at the tertiary carbon, amounts to about 48 per cent on a molar basis. Since there are present in the molecule thirty secondary hydrogen atoms and six primary hydrogen atoms, and the primary degradation products contain many secondary hydrogen atoms, a highly selective attack at the tertiary hydrogen is demonstrated.

It may be noted that the keto acid and monobasic acid from oxidation of acid VII are obtained in similar yields, as would be expected, since these products result from cleavage of the bond to the tertiary carbon on the side remote from carboxyl. In contrast, the ketone and dibasic acid resulting from cleavage in the alternate position at the tertiary carbon were detected in a ratio of about 1 : 22. Furthermore, the yield of dibasic acid is more than twice that of the monobasic acids. These data clearly indicate that carboxyl has a significant stabilizing effect against attack by the oxidizing agent, and the magnitude of the effect suggests that the protection afforded by carboxyl extends beyond the *alpha* position.

The data in Table 2 show that the protecting effect of carboxyl extends as far as the *gamma* position, at which point it ceases rather abruptly. Yields of 2-tetradecanone

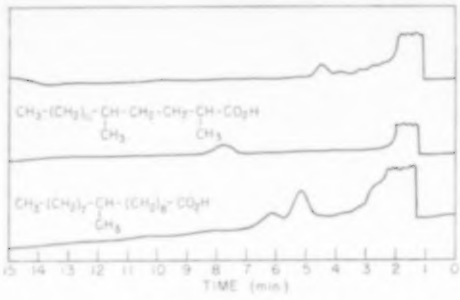


FIG. 1. Recorder tracings from gas chromatography of oxidative degradation products. There was used a 3 m × 15 mm o.d. column of Pyrex glass containing as partitioning agent high vacuum silicone grease dispersed on 30–60 mesh Celite fire-brick (4 parts grease : 10 parts fire-brick); helium pressure was 18·5–22 cm of mercury; flow rate was 150–180 ml/min; temp for upper and lower tracings was 280°, for center tracing 260°. The initial off-scale band in each tracing is due to the benzene used as solvent for the material injected.

Lower curve: Esters of acids from degradation of 10-methyloctadecanoic acid. Retention times for major bands were 2 : 40 (min, sec) for methyl octanoate, 5 : 10 for dimethyl azelate, and 6 : 07 for methyl 10-oxohendecanoate. For quantitative determination of octanoate, its band was resolved from the solvent band by chromatography at lower temperature.

Center curve: Neutral material from degradation of 2,5-dimethylheptadecanoate; retention time for 2-tetradecanone was 7 : 45.

Upper curve: Esters of acids from degradation of 2,5-dimethylheptadecanoate. Retention time for methyl dodecanoate was 4 : 50. Area under the largest secondary band (at 3 : 45) is about one-fifth that of the dodecanoate band. At the edge of the figure, the band for ester of starting acid is developing.

and dodecanoic acid from 2,5-dimethylheptadecanoic acid are about half the yields of cleavage products from the 10-methyl acid, and the yields from the 6-methyl acid (cf. Table 1) are as good as those from the 10-methyl acid. The near normal yield of ketone obtained from the α,β-unsaturated acid (last entry in Table 2) is of interest in connection with the mechanism of the oxidation. This yield also indicates that the

TABLE 2. DEGRADATION OF ACIDS WITH BRANCHES NEAR CARBOXYL

Acid oxidized	Yield (wt. %) of degradation products[a]	
	Ketone	Acid
10-Methyloctadecanoic	1·0	9·8
2-Methyloctadecanoic	0·2	nil
3-Methyloctadecanoic	*b*	*b*
4-Methyloctadecanoic	*b*	*b*
2,4-Dimethyldocosanoic	*b*	*b*
2,5-Dimethylheptadecanoic	0·4	4·7
2,4-Dimethyl-2-docosenoic	0·6	0·05[c]

[a] The ketone and the ester of the acid from the terminal portion of the molecule were determined by gas chromatography. No effort was made to isolate the lower molecular weight fragments from the carboxyl end of the acid degraded. Thus, expected degradation products from 3-methyloctadecanoic acid would be 2-heptadecanone and pentadecanoic acid.

[b] Many small peaks in gas chromatography tracing, with no dominant one.

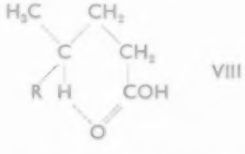
[c] In this degradation, there was also detected 6·3 % yield of 2-methyleicosanoic acid, from cleavage at the double bond.

tertiary 4-position is attacked about as rapidly as the double bond; otherwise, the yield of ketone could hardly be greater than that from the 2-methyl acid.

In considering a mechanism for the oxidation, cognizance must be taken, not only of the data secured in the present investigation, but also of the considerable evidence supporting the thesis[7] that oxidations in acid solution are ionic in character and the attacking species in such oxidations is positive. In a solution of chromic anhydride in acetic acid, the most probable oxidizing species[7] is $^{+}CrO_3H$. Since Bartlett *et al.*[8] have shown that a carbonium ion very rapidly removes a hydride ion from the tertiary position in isopentane, the initial step in the presently investigated oxidation may be reasonably formulated as follows:

The higher electron density at the tertiary hydrogen, as well as the greater stability of the tertiary carbonium ion, would combine to promote the selective attack that is observed at the tertiary position. Loss of a proton by the initially formed carbonium ion would lead to a mixture of alkenes, with the higher energy methylene isomer in smaller amount. Subsequent oxidation of the alkenes would lead to the observed degradation products, with a smaller amount of the keto acid resulting from elimination of methyl.

If this proposed mechanism for the oxidation be correct, then an electron-withdrawing group such as carboxyl should indeed reduce the reactivity of hydrogens on the adjacent *alpha* position; however, such a direct inductive effect should drop off rapidly with distance and become negligible at the *gamma* position. The experimental observation that the hydrogens at the *gamma* position are no more reactive than those at the *alpha* position indicates an interaction between carboxyl and hydrogen at the *gamma* position. Several properties of fatty acids and derivatives have been successfully correlated[9] on the basis of a quasi ring conformation resulting from hydrogen bonding of the *gamma* hydrogen with carboxyl oxygen. For a γ-methyl acid, this ring would take the form of VIII, wherein the tertiary hydrogen should be



VIII

protected from attack by the oxidizing agent. Since hydrogens in the *beta* position are also relatively inert to oxidative attack, it is suggested that the inductive effect of carboxyl is an important factor in stabilizing the positions included in the quasi ring. Furthermore, the slightly reduced reactivity of hydrogens at the *delta* position may well result from the proximity of this position to carboxyl, in the quasi ring structure.

[7] L. S. Levitt, *J. Org. Chem.* **20**, 1297 (1955).
[8] P. D. Bartlett, F. E. Condon and A. Schneider, *J. Amer. Chem. Soc.* **66**, 1531 (1944).
[9] J. Cason and G. Sumrell, *J. Org. Chem.* **16**, 1177 (1951); H. A. Smith and J. P. McReynolds, *J. Amer. Chem. Soc.* **61**, 1963 (1939).

VOL. 7 1959

If a double bond is introduced in the α,β-position in a fatty acid, and it has the *trans* configuration, a quasi ring such as indicated in VIII cannot form and the γ-hydrogen should lose its protection. The 2,4-dimethyl-2-docosenoic acid, whose degradation is indicated in Table 2, has the *trans* configuration,[10] and it will be noted that a relatively good yield of ketone was obtained on oxidation, in contrast to the behavior of the saturated acid. Failure to obtain significant amounts of octadecanoic acid from degradation of the unsaturated acid would be expected because the carbonium ion proposed as the first intermediate in the oxidation would have double bond character at the β,γ-position. Pertinent resonance forms would be the following:

In order to verify the greater susceptibility to attack of hydrogens beyond the *gamma* position, certain dibasic acids have been subjected to the same conditions of oxidation that are used for degradation of branched-chain compounds. In the case of azelaic acid, $HO_2C{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CO_2H$, the center carbon is the only one beyond the *gamma* positions, hence dominant degradation products should be succinic and glutaric acids, resulting from cleavage on either side of the central carbon. As judged by gas phase chromatography, 84 per cent of the dibasic acid survived the oxidative treatment. The total area under the bands resulting from degradation products was divided as follows:[11] succinic, 33 per cent; glutaric, 39·5 per cent; adipic, 14·5 per cent; pimelic, 11·8 per cent; suberic, 1·2 per cent. Since the yield of adipic acid, which results from attack at the *beta* or *gamma* position, is scarcely more than one-third the yield of glutaric acid, it may be concluded that the prime source of glutaric and succinic acids is attack at the single *delta* position.

Oxidation of hendecanedioic acid, containing three carbon atoms beyond the *gamma* positions, was especially striking. The results of this oxidation are summarized in Table 3. It may be noted that the degradation products which may result from attack at the *delta* or *epsilon* position are detected in twice the quantity of those resulting from attack at the *gamma* or *delta* position. Products resulting from attack at positions closer to carboxyl than *delta* have become insignificant.

Oxidation of a normal monobasic acid is not subject to the selectivity observed for higher dibasic acids, for any hydrogens beyond the *gamma* position are equally subject to attack. This was observed experimentally by oxidation of dodecanoic acid. Bands of similar size were observed for the homologs from succinate (and heptanoate) to suberate. Recovery of dodecanoic acid was 75 per cent. Azelate was under the very large dodecanoate band and sebacate was on the trailing edge of it.

One aspect of the results obtained by degradation of normal dibasic acids is of importance in connection with interpretation of the results of degradation of higher molecular weight branched-chain compounds. If a branch or branches are so located that a primary degradation product is a normal dibasic acid with nine or more carbons,

[10] J. Cason and M. J. Kalm, *J. Org. Chem.* **19**, 1947 (1954).

[11] The ratio of moles of acids will be slightly more favorable to the lower molecular weight acids than the ratio of areas; however, this correction is small enough to be of no significance to the present discussion. It has been reported [R. H. Eastman, *J. Amer. Chem. Soc.* **79**, 4243 (1957)] that the weight ratio of two components is equal to the product of the ratio of areas under the bands and the ratio of the square root of the respective molecular weights. Thus, the correction factor for molar ratios would be the inverse ratio of square root of molecular weights.

TABLE 3. OXIDATIVE DEGRADATION OF HENDECANEDIOIC ACID

1 2 3 4 5 6 7 8 9 10 11

$\alpha\ \beta\ \gamma\ \delta\ \epsilon\ \delta\ \gamma\ \beta\ \alpha$

$HO_2C—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CH_2—CO_2H$

Acid from degradation	Position attacked	Per cent of total area[a]
glutaric (C_5)	δ or ϵ	28
adipic (C_6)	δ or ϵ	34·5
succinic (C_4)	γ or δ	12
pimelic (C_7)	γ or δ	18
suberic (C_8)	β or γ	3
azelaic (C_9)	α or β	3
sebacic (C_{10})	α	1·5

[a] Data recorded are referred to the total area ascribed to degradation products, which was 23 per cent of total area under all bands; the remaining 77 per cent was under the band due to recovered hendecanedioic acid. For relationship of molar ratio to area ratio, refer to footnote 11.

the small amount of further degradation of this product becomes selective, as has been described above. For example, if azelaic acid is a primary degradation product, further degradation of this dibasic acid yields principally succinic and glutaric acids. The gas chromatography bands for esters of these acids then become larger than bands from the other secondary degradation products, and there may arise the question that these bands represent monobasic esters (see below) from a primary degradation or products arising from impurities present in small amounts. This uncertainty may usually be resolved by consideration of the degradation expected from the dibasic acid obtained as a major chromatography band, and noting the ratio of the major band to the larger satellite bands.

Another factor of importance in interpreting gas chromatography of degradation products on silicone grease is the coincidence of bands due to dibasic esters and monobasic esters. Dimethyl succinate coincides with methyl heptanoate, glutarate with octanoate, etc. This factor rarely causes uncertainty because of the relationship of ketone to monobasic acid and keto acid to dibasic acid. If difficulty does arise in complicated degradation patterns, or from selective degradation of a dibasic acid, the distinction between monobasic and dibasic acids may be made by comparison of retention times for methyl and ethyl esters. The shift in retention time in going from methyl to ethyl esters will obviously be greater for the dibasic acid. In cases of remaining uncertainty, butyl esters may be invoked. Furthermore, chromatography on the partitioning agent known as Reoplex-400 (Geigy) shifts the dibasic esters to longer retention times in relation to the monobasic esters.

Since vigorous oxidation of other aliphatic structures leads to acids, it may be assumed that the presently investigated method is applicable to degradation of branched aliphatic structures containing various functional groups. As a confirmation of the utility of the method for degradation of saturated hydrocarbons, oxidation of the symmetrically branched alkane, 9,14-dimethyldocosane, $C_8H_{17}—CH(CH_3)—(CH_2)_4—CH(CH_3)—C_8H_{17}$, was examined. Major chromatography bands were

observed for three of the four products resulting from a single cleavage of the chain at the tertiary position: octanoate, decanone, and 5-methyl-tridecanoate (retention time between normal tridecanoate and normal tetradecanoate). The band for 7-methyl-2-pentadecanone was not observed (and hardly expected since a normal ketone is obtained only in low yield). A smaller band was observed for succinate, formed by successive chain cleavages. Another smaller band at slightly longer retention time than octanoate was probably due to the δ-ketocaproic acid. Thus, the structure of the disubstituted alkane could be deduced from the degradation products obtained from oxidation of a 22 mg sample. The three major bands were detected from oxidation of a 6·5 mg sample.

As an example of a more complicated structure, there was investigated the degradation of 4,8,12-trimethyloctadecanoic acid. As usual, no degradation products were observed from cleavage at the 4-position. From cleavage at the 8-position, there were observed in the complicated chromatogram from degradation esters strong bands corresponding to 4-methylpimelic acid and to 4-methyl-8-oxononanoic acid. There was also observed in the neutral fraction a strong band corresponding to 6-methyl-2-dodecanone (slightly shorter retention time than a normal tridecanone). From cleavage at the 12-position, bands were observed corresponding to 2-octanone and hexanoic acid; however, these bands were weaker than normally obtained from primary degradation products. Several minor bands were probably due to products of successive cleavages; however, these could not be reliably distinguished from bands due to secondary degradation products. This latter development, also observed in the degradation of 9,14-dimethyldocosane, may well be an advantage in degradation of complicated molecules, for it simplifies detection of products from a single cleavage.

EXPERIMENTAL

Materials. The branched-chain acids and the branched hydrocarbon used for oxidation were samples of compounds prepared previously in these laboratories in connection with the program of synthesis of branched-chain acids. Acetic acid used as solvent for the oxidations had been distilled from potassium permanganate. The chromic anhydride (CrO_3) used as oxidant was a commerical product.

Gas phase chromatography. The partitioning agent used in all chromatographic analyses was Dow-Corning high vacuum silicone grease, dispersed on 30–60 mesh Celite fire-brick or on the similar material marketed as "Chromosorb" (Johns–Manville). The ratio of grease to Celite was 4 : 10. For relatively large-scale runs (50–300 mg) in which yields of oxidation products were determined, there was used the rather large column described in connection with Fig. 1. For all runs on smaller samples, there was used a 1·5 m × 8 mm o.d. Pyrex glass column for chromatography at temp of 170–290°, and a similar 2 m column for temp below 170°. Thermal detection cells utilizing a thermistor were employed. Limit of detection was 1–50 μg, depending on the temp; below 200°, limit of detection was <2 μg.

In most instances, identification of degradation products rested on coincidence of the retention time with that of a known sample, although 2-tetradecanone from oxidation of 6-methyloctadecanoic acid was collected and found to have the I.R. spectrum of a ketone. Since neutral and acidic products were separated before chromatography, there seems no possibility of uncertainty concerning the identity of products giving major bands (distinction between di-esters and mono-esters has been discussed earlier). In addition, degradation of numerous compounds with a single branch in a known position has yielded no major bands except those corresponding to expected degradation products.

On each occasion that degradation products were chromatographed, known compounds were chromatographed in sequence; however, it is not necessary that the known compounds be identical with the degradation products. Three or more homologs of the degradation products, injected as a mixture, may be used to locate retention times at least as accurately as may be accomplished by

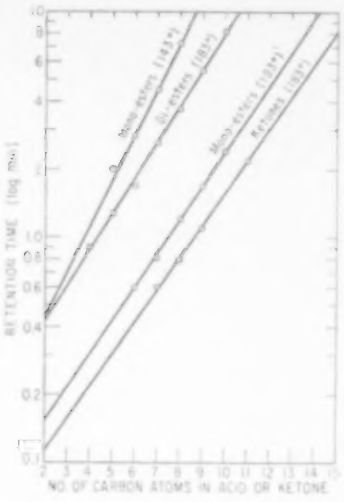


FIG. 2. Retention times in gas chromatography of homologous series. The essentially parallel lines for the different homologous series are characteristic, as is the increased slope at lower temp. At 183°, in sequential runs, retention time for methyl 10-oxohendecanoate was 7·8 min.

injection of only the known compounds. Sample semi-log plots used for location of retention times are presented in Fig. 2. Compounds with a branched chain, as encountered in degradation of 4,8,12-trimethyloctadecanoic acid, may be located with sufficient accuracy by reference to such plots. In the range of 8–20 carbon atoms, a compound with a single small branch falls between its normal isomer and the next lower homolog, usually about midway between. In tests of C_{18} normal ketones, the retention time was found to decrease slightly as the keto progressed from the 2-position to the center of the chain, with the maximum shift no more than one-third the contribution of a methylene group. A keto ester is located at a very slightly shorter retention time than the di-ester of a dibasic acid with one less carbon (a sample of synthetic methyl 10-oxohendecanoate falls at a slightly shorter retention time than dimethyl sebacate). It follows that, even with a methyl branch, the di-ester and keto ester obtained by degradation of a branched-chain acid are readily separable and recognizable by the chromatography procedure.

Carboxylic acids may be chromatographed on the silicone grease partitioning agent; however, esters give stronger signals with a thermal detector, as well as sharper, more easily resolved bands.

Procedure for oxidative degradation. There is described the procedure regarded as the best of the various modifications examined. It provides for recovery of rather water-soluble products (such as glutaric acid), as well as rather volatile components (such as butanone).

A 10 mg sample of methyl 10-methyloctadecanoate (or the free acid) was added to a solution of 20 mg of chromic anhydride in 1 ml of glacial acetic acid. The resultant solution was heated under a water-cooled reflux condenser for 2–3 hr in a bath maintained at 65–70°. If a branched-chain compound is being oxidized, the initially red-brown solution becomes green after about 1 hr. To the cooled reaction mixture there was added 5% KOH until phenolphthalein indicator was turned pink (about 20 ml of alkali required). The resultant alkaline solution was continuously extracted with about 40 ml of ether for several hours. After the ether extract had been dried over anhydrous magnesium sulfate solvent was distilled through a half-meter column of the simple Podbielniak design.[12] A 10 ml pointed flask was used for the final stages of the distillation so that the residue might be brought nearly to dryness, then washed down with ether or benzene to about 0·2 ml volume in the tip of the flask. This concentrated solution was injected for gas chromatography of the neutral product. A volume of 10–50 μl is usually a satisfactory amount for injection.

[12] A satisfactory column is similar to that which has been described in detail by J. Cason and H. Rapoport in *Laboratory Text in Organic Chemistry* pp. 237–243. Prentice-Hall, Englewood Cliffs (1950). For present purposes, a heated head and jacket are unnecessary.

The alkaline solution, from which neutral material had been extracted, was concentrated to dryness under reduced pressure, and the residual salt was dried at 100° and 10–20 mm pressure for about 10 min. To the dry salts was added 10 ml of anhydrous methanol containing 20% by weight of conc H_2SO_4. This mixture was heated under a water-cooled reflux condenser in a bath at 45–50° for 3 hr, during which period there was added in three increments a total of 1 ml of acetone dimethyl acetal (2,2-dimethoxypropane). The cooled reaction mixture was placed in a continuous extractor containing 20 ml of water and neutralized to pH 7 with 10% KOH. The esters were continuously extracted with about 50 ml of ether,[13] and the extract was dried and concentrated for chromatography as described for the ketone fraction.

If a compound contains more than one branching group it is probably an advantage to use a slightly larger ratio of oxidizing agent, but not in proportion to the number of branches. For 4,8,12-trimethyloctadecanoic acid, containing two branches susceptible to selective attack, the best run was one in which there was used 40 mg of chromic anhydride for 16·5 mg of the acid.

[13] Unless low-boiling esters are expected as degradation products, this extraction is accomplished more reliably with benzene. Ether extracts considerable water from the aqueous methanol solution.

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VOL. 7 1959

FURAN TETRACARBOXYLIC ACID

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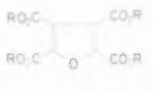
Abstract—Furan tetracarboxylic acid is a surprisingly strong acid. It forms well defined salts with a variety of bases. Its structure, and that of an intermediate in its preparation, is discussed in relation to its ultra-violet and infra-red spectra.

DURING the course of another investigation in which furan tetracarboxylic acid (F.T.C.A., I; R = H) was required as an intermediate, we were attracted to the properties of this acid. It may conveniently be prepared[1–4] by the bromination of ethyl sodiooxaloacetate to give a tetracarboxylic ester variously described as II,[1] III,[2] and IV,[4] followed by treatment of the tetraester with sulphuric acid to give I (R = Et). Of these structures IV is to be preferred since the tetraester gives no ferric reaction, but it shows strong hydroxyl absorption at 3500 cm^{-1} in the infra-red. Again, the tetraester shows strong absorption at 1775 and 1765 cm^{-1} which may be attributed to unconjugated ester groups, 1704 cm^{-1} arising from a conjugated ester and a fairly strong maximum at 1650 cm^{-1}. The intensity of the latter maximum is characteristic[5] of the C=C—O group. Thus dihydropyran shows a strong maximum at 1650 cm^{1}, and compound V[5] shows a strong maximum at 1627 cm^{-1} attributable to the C=C—O group. Furthermore the tetraester absorbs maximally at 2470 Å, log ε 3·86 in good agreement with the maximum absorption of V at 2480 Å, log ε 4·1.

However the tetraester does not absorb bromine and only decolourizes permanganate slowly. These may be characteristics of the unsaturated system in IV, although maleic ester reacts instantaneously with permanganate. Furthermore a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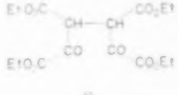
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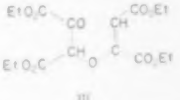
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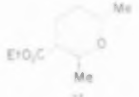
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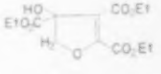
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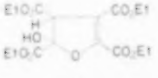
VIII


IX

[1] H. Sutter, *Liebigs Ann.* **499**, 56 (1932).
[2] T. Reichstein, A. Grussner, K. Schindler and E. Hardmeyer, *Helv. Chim. Acta* **16**, 276 (1933).
[3] H. Gilman, H. J. Oatfield and W. H. Kirkpatrick, *Proc. Iowa Acad. Sci.* **40**, 113 (1933).
[4] A. P. Dunlop and C. D. Hurd, *J. Org. Chem.* **15**, 1160 (1950).
[5] F. E. Bader, *Helv. Chim. Acta* **36**, 215 (1953).

compound of structure IV might be expected to be more unstable than is the case in view of its β-hydroxyester structure and the stability of the furan system. We therefore suggest that structure VI should not be overlooked pending the completion of further work.

A structure analogous to IV namely VII is preferred[cf.6] for the tricarboxylic ester (which shows similar infra-red characteristics to IV) formed by the condensation of ethyl bromopyruvate and ethyl sodio-oxaloacetate. The conversion of the tricarboxylic ester to triethyl furan-2:3:4-tricarboxylate with sulphuric acid eliminates the alternative structure VIII. The structure IX for the tetraester discussed above can by analogy be reasonably eliminated.

Hydrolysis of I(R = Et) to I(R = H) is usually performed[2] with hydrochloric acid. We used alcoholic potash for this purpose and after acidification of the alkaline solution a crystalline monopotassium salt of F.T.C.A. was obtained instead of the expected acid. The salt is not very soluble (14·54 g/l. at 18°) in cold water, and it may be crystallized from hot water. It may be crystallized unchanged from concentrated hydrochloric acid or 50 per cent sulphuric acid, but it is decomposed by 20 per cent perchloric acid. F.T.C.A. may however be quantitatively recovered from the monopotassium salt on passage in aqueous solution, or better in a solution of sodium carbonate, through a column of Zeo–Karb 225 ion exchange resin.

F.T.C.A. is a strong acid (see below) and it forms a series of well defined mono salts, which are stable to hydrochloric acid, with a variety of bases. The acid itself is very soluble in water, but it may conveniently be recrystallized from concentrated hydrochloric acid, in which it is largely unionised.

The apparent dissociation constants (pK) of F.T.C.A. were determined by the potentiometric method, the pH changes being followed by means of a Radiometer pH meter 23 using a type G 202 B glass electrode and a saturated potassium chloride–calomel electrode. Dissociation constants were measured only at one concentration of F.T.C.A., but change of concentration is not likely seriously to affect their order of magnitude. Table 1 summarizes the dissociation constants of F.T.C.A. and a number of analogous acids

TABLE 1

Acid	K_1	K_2	K_3	K_4	K_5	K_6
F.T.C.A.	$4{\cdot}2 \times 10^{-1}$ ($pK_1 = 1{\cdot}37$)	$8{\cdot}0 \times 10^{-2}$ ($pK_2 = 2{\cdot}1$)	$1{\cdot}86 \times 10^{-2}$ ($pK_3 = 3{\cdot}73$)	$1{\cdot}96 \times 10^{-7}$ ($pK_4 = 7{\cdot}7$		
Phthalic[7]	$1{\cdot}05 \times 10^{-3}$	$5{\cdot}2 \times 10^{-6}$				
Pyromellitic[7]	$1{\cdot}2 \times 10^{-2}$	$1{\cdot}34 \times 10^{-3}$	$3{\cdot}2 \times 10^{-5}$	$2{\cdot}35 \times 10^{-6}$		
Prehitnic[7]	$4{\cdot}2 \times 10^{-2}$	$3{\cdot}1 \times 10^{-4}$	$3{\cdot}6 \times 10^{-5}$	$1{\cdot}55 \times 10^{-6}$		
Mellophanic[7] (1l2:3:4)	$8{\cdot}8 \times 10^{-2}$	$5{\cdot}6 \times 10^{-4}$	$1{\cdot}87 \times 10^{-5}$	$6{\cdot}1 \times 10^{-7}$		
pentacarboxylic[7]	$1{\cdot}6 \times 10^{-2}$	$1{\cdot}85 \times 10^{-3}$	$1{\cdot}08 \times 10^{-4}$	$5{\cdot}6 \times 10^{-6}$	$3{\cdot}5 \times 10^{-7}$	
Mellitic[7]	$4{\cdot}0 \times 10^{-2}$	$6{\cdot}4 \times 10^{-3}$	$4{\cdot}9 \times 10^{-4}$	$1{\cdot}65 \times 10^{-5}$	$1{\cdot}28 \times 10^{-6}$	$1{\cdot}1 \times 10^{-7}$
Maleic[8]	$1{\cdot}2 \times 10^{-2}$	$6{\cdot}0 \times 10^{-7}$				

Concentration of F.T.C.A. = 0·001 M N/5 NaOH used as titrant

[6] E. C. Kornfield and R. G. Jones, *J. Org. Chem.* **19**, 16 (1954).
[7] W. R. Maxwell and J. R. Partington, *Trans. Faraday Soc.* **33**, 670 (1937).
[8] W. L. German, G. H. Jeffery and A. I. Vogel, *Phil. Mag.* **22**, 790 (1936).

VOL. 7 1959

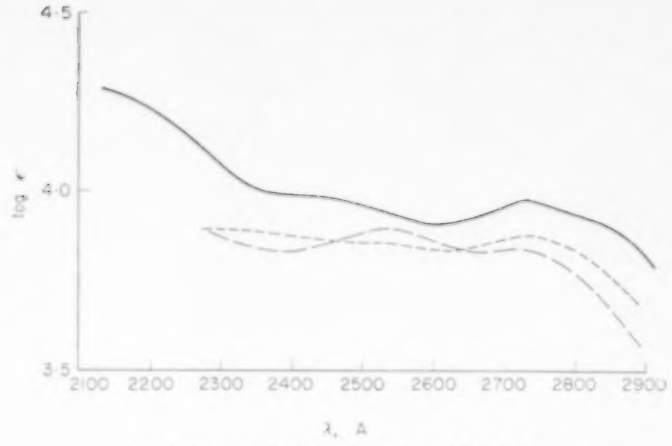


FIG. 1. Ultra-violet light absorption of F.T.C.A. in water.
– – – 0·00012 mole/l; λ_{max} 2520 Å. log ε 3·90 inflex. 2720 Å
. . . . . 0·000037 mole/l; λ_{max} 2720 Å. log ε 3·87
——— 0.000012 mole/l; λ_{max} 2720 Å. log ε 3·97

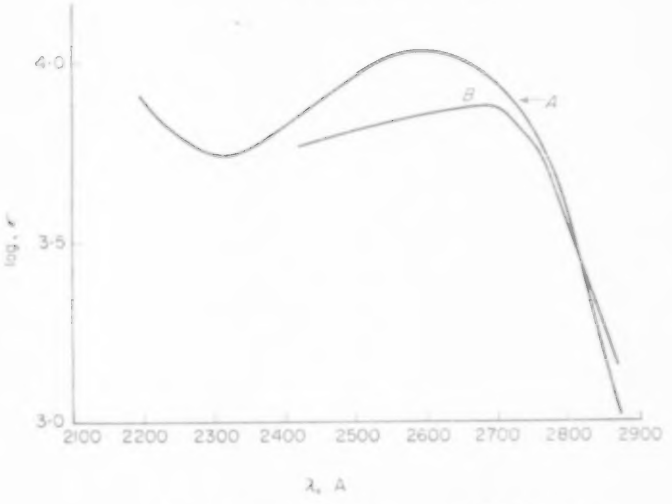


FIG. 2. Ultra-violet light absorption of F.T.C. A.
A—In N HCl λ_{max} 2590 Å log ε 4·03.
B—In MeOH λ_{max} 2700 Å log ε 3·89.

It is clear from the above data that F.T.C.A. is ten times as strong as mellitic acid and considerably stronger than maleic acid. F.T.C.A. is in fact comparable in strength with dichloroacetic acid (p*K* 1·29).[9]

As is only to be expected aqueous solutions of F.T.C.A. do not obey Beer's law. The values of p*K* given above indicate that three of the carboxyl groups are completely ionized at pH 7. Figs. 1 and 2 show the ultra-violet spectrum of the acid and its tetramethyl ester under various conditions. With change in concentration the acid

[9] L. F. Fieser and M. Fieser, *Organic Chemistry* (3rd Ed.) p. 163. Reinhold, New York (1956).

shows the development and suppression of peaks at about 2520 and 2720 Å as is only to be expected with change in the ionic species present. The tetramethyl ester shows a single maximum at 2590 Å. Dissolved in N-hydrochloric acid, in which one carboxyl alone is ionized to a slight extent and the others unionized, F.T.C.A. shows a single maximum at 2590 Å, and in aqueous solution at a concentration of 0·00012 mole/l. the acid shows two maxima, one at 2520 Å. The maximum in the 2520 to 2590 Å range can only be attributed to a largely unionized species. At all concentrations of F.T.C.A. used and in methanol, F.T.C.A. shows a maximum at 2700–2720 Å which we attribute to an ionised form.

The spectra of other furan carboxylic acids warrant comparison. Furan 2-carboxylic acid in water absorbs[10] maximally at 2450 and 2150 Å. In ethanol[11] the longer wavelength absorption occurs at 2480 Å whilst in hexane in which the acid is is unionized this band occurs at 2580 Å. Furan 2:5-dicarboxylic acid in aqueous solution absorbs[11] at 2625, (2370), and 1920 Å. Thus in water there is a bathochromic effect of about 175 Å in passing from the mono to the dicarboxylic acid. A further bathochromic shift of about 220 Å takes place in passing from the latter to the tetracarboxylic acid. This information is summarised in Table 2.

Table 2. Ultra-violet spectra of furan carboxylic acids and derivatives

	λ_{max} (Å) in H_2O	λ_{max} (Å) in EtOH	λ_{max} (Å) in hexane	λ_{max} (Å) in N HCl
Furan 2-carboxylic acid	2450, 2150	2480	2580	
Furan 2,5-dicarboxylic acid	2625, (2370), 1920			
Furan 2,3,4,5-tetra-carboxylic acid	2520, 2720	2720[a]		2590
Tetraethyl furan-2,3,4,5-tetracarboxylate		2590		

[a] Measured in MeOH

In the infra-red F.T.C.A. shows (in paraffin) a different spectrum from its mono potassium salt. The acid shows only weak absorption at 3500 cm^{-1} but strong absorption at 2466 cm^{-1} and 2375 cm^{-1} and medium strong absorption at 1887 cm^{-1}. Considerable hydrogen bonding is thus indicated. Strong maxima at 1694 and 1643 cm^{-1} shown by the acid may be assigned to hydrogen bonded carboxyl, whilst strong bands at 1606 and 1515 cm^{-1} may be attributed to aromatic type unsaturation.

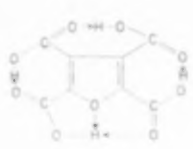
In contrast to the acid, the mono potassium salt shows stronger absorption at 3570 cm^{-1}. Maleic acid and its mono potassium salt behave similarly.[12] However the potassium salt of F.T.C.A. shows some absorption at 2300 cm^{-1} not displayed by potassium hydrogen maleate. Hydrogen bonding of a type different from that shown by the latter is therefore present in the former. The potassium salt of F.T.C.A. shows strong absorption at 1734 and 1720 cm^{-1} absent from F.T.C.A. and potassium

[10] G. Mackinney and O. Temmer, *J. Amer. Chem. Soc.* **70,** 3586 (1948).
[11] K. W. Hausser, R. Kuhn, A. Smakula, and A. Deutsch, *Z. Phys. Chem.* **29,** 378 (1935B).
[12] H. M. E. Cardwell, J. D. Dunitz and L. E. Orgel, *J. Chem. Soc.* 3740 (1953).

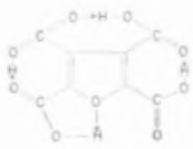
hydrogen maleate, which must be attributed to carboxyl. Other strong bands shown by the potassium salt of F.T.C.A. are at 1575 cm^{-1} (CO_2^-) and at 1556 and 1534 cm^{-1} in the region of absorption by aromatic type unsaturation.

The tetramethyl ester of F.T.C.A. when examined in paraffin shows strong bands at 1766, 1747 and 1728 cm^{-1} and a weaker band at 1759 cm^{-1}. These bands can only be attributed to the methoxycarbonyl groups. A fairly strong band at 1612 cm^{-1} indicates aromatic type unsaturation, but this band is less intense than the corresponding band in F.T.C.A. The displacement of this band from around 1610 cm^{-1} in ester and acid to 1556 cm^{-1} in the salt has some significance not obvious to us at present.

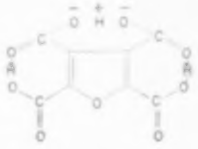
The considerable hydrogen bonding shown by F.T.C.A. can be best accommodated in the symmetrical structure X but models show that the distance shown by the broken arrow is too great for hydrogen bond formation. All the other hydrogen bonds are capable of formation. F.T.C.A. may therefore exist as XI. Whilst it is very likely that the carboxyl group in the 2-position is the strongest of the four and therefore will initially form the anion we feel that the most likely structure for the potassium salt is XII incorporating the suggestion of Cardwell *et al.*[12] Besides being the most symmetrical form XII has two "exposed" carbonyl groups which may be responsible for the bands shown by the potassium salt in the infra-red at 1734 and 1720 cm^{-1}. Full elucidation of fine structure of the acid and salt will however have to await their X-ray examination.



X



XI



XII

EXPERIMENTAL

Salts of furan tetracarboxylic acid. A mixture of molar quantities of the acid and the base was heated with sufficient water to effect solution at 100°. The solution was cooled and the salt was deposited. It was collected, washed with ice-cold water and dried. Alternatively, water insoluble bases were dissolved in a minimum of conc HCl, a molar quantity of furan tetracarboxylic acid was added, the mixture was heated to 100°, and water was added at this temp until solution was effected. In all cases except that of the dimethylformamide salt the mono salt was formed whether the reaction was carried out either in presence or absence of HCl. With dimethylformamide the mono salt was obtained when HCl was present, and a di salt when mineral acid was absent.

Potassium salt. Ethyl furan tetracarboxylate (I; R = Et)(10 g) was refluxed for 1 hr with a solution of potassium hydroxide (70 g) in water (200 cc). The solution was filtered and acidified to congo red with HCl. On cooling the hydrated mono potassium salt was deposited (8·5 g; 95%). Crystallization from water gave long needles, m.p. 261° (dec) (Found, without drying to constant weight, C, 30·5; H, 2·9. E, 103. $C_8H_3O_9K$. $2H_2O$ requires: C, 30·2; H, 2·2% E, 106. Found after drying at 160° in a vacuum C, 33·4; H, 1·0; K, 13·8. $C_8H_3O_9K$ requires: C, 34·0; H, 1·1; K, 13·8%).

Furan tetracarboxylic acid. The potassium salt (4 g) was dissolved with 3 g sodium carbonate in water (100 cc) and passed through a column of Zeo–Karb 225 which was then washed with water. Concentration of the eluate in a vacuum gave furan tetracarboxylic acid (3.1 g), m.p. 235° (dec), which on crystallization gave the acid as rhombs, m.p. 248° (dec).[2]

Table 3. Salts of furan tetracarboxylic acid

Base	M.p. and crystalline form of salt		
Rb	275° (dec)	needles (H_2O)	C, 28·2; H, 1·0. $C_8H_2O_9Rb_2\frac{1}{2}H_2O$ requires: C, 28·4; H, 1·2%
$MeNH_2$	237–238°	needles ($MeOH/H_2O$)	C, 38·9; H, 3·6. $C_9H_9O_9N$ requires: C, 39·3; H, 3·3%
$EtNH_2$	203–204°	needles (MeOH)	C, 41·3; H, 3·8; N, 5·1. $C_{10}H_{11}O_9N$ requires: C, 41·5; H, 3·8; N, 4·8%
$NH_2(CH_2)_2NH_2$	262° (dec)[a]	rhombs (H_2O)	C, 39·7; H, 3·3; N, 5·2. $C_{18}H_{16}O_{18}N_2$ requires: C, 39·4; H, 2·9; N, 5·1%
NH_2NH_2	212° (dec)	needles ($MeOH/H_2O$)	C, 31·5, 31·8; H, 3·7, 3·7. $C_8H_8O_9N_2\ 1\frac{1}{2}\ H_2O$ requires: C, 31·7; H, 3·6%
$NH_2NHCONH_2$	200–201° (dec)	needles (H_2O)	C, 33·4; H, 2·9. $C_9H_6O_{10}N_2$ requires: C, 33·9; H, 2·8%
NH_2CONH_2	170°	needles (MeOH)	C, 32·8; H, 3·1. $C_9H_6O_{10}N_2\ 1\frac{1}{2}\ H_2O$ requires: C, 32·7; H, 3·3%
$HCONMe_2$	251° (dec)[b]	prisms ($MeOH/H_2O$)	C, 41·8; H, 3·9. $C_{11}H_{11}O_{10}N$ requires: C, 41·6; H, 3·5%
	190–191°[c]	needles (EtOH)	C, 43·1; H, 4·6. $C_{14}H_{14}O_{11}N_2$ requires: C, 43·1; H, 4·6%
Piperidine	196–197°	needles (MeOH)	C, 47·8; H, 4·7. $C_{13}H_{14}O_9N$ requires: C, 47·4; H, 4·6%
Pyridine	250° (dec)	needles ($MeOH/H_2O$)	C, 47·4; H, 2·7. $C_{13}H_5O_9N\ \frac{1}{2}\ H_2O$ requires: C, 47·0; H, 3·0%
Quinoline	207–208°	needles (C_6H_6)	C, 54·3; H, 3·2. $C_{17}H_{11}O_9N$ requires: C, 54·7; H, 3·0%
$C_6H_5NH_2$	171° (dec)	prisms (H_2O)	C, 50·5; H, 3·6. $C_{14}H_{11}O_9N$ requires: C, 49·9; H, 3·3%
C_6H_5NHMe	216°	rhombs ($MeOH/H_2O$)	C, 51·6; H, 4·0. $C_{15}H_{13}O_9N$ requires: C, 51·3; H, 3·7%
$pMeC_6H_4NH_2$	187° (dec), loses H_2O at 150°	needles (H_2O)	C, 49·6; H, 4·5. $C_{15}H_{13}O_9NH_2O$ requires: C, 48·9; H, 4·0%

[a] refers to a bis salt of $NH_2(CH_2NH_2)_2$
[b] refers to a mono $HCONMe_2$ salt
[c] refers to a di $HCONMe_2$ salt
All salts were dried on the water bath at about 90°

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THE DECOMPOSITION OF SULPHONYL-HYDRAZONE SALTS—I

MECHANISM AND STEREOCHEMISTRY

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Abstract—The rate-determining stage in the Bamford–Stevens reaction is shown to be a unimolecular elimination from the anion of the sulphonylhydrazone. This gives, apparently in all cases, a secondary aliphatic diazo-compound, which then undergoes thermal decomposition. Such diazo-compounds may decompose in solvents rich in available protons, such as were originally used by Bamford and Stevens, mainly via the diazonium cation, and the reaction then degenerates into a variant of the normal deamination reaction. Acetamide is a convenient solvent for minimizing this effect, and gives higher yields of hydrocarbon products.

BAMFORD and Stevens[1] recently described a reaction in which toluene-*p*-sulphonylhydrazones were heated with the sodium derivative of ethylene glycol, in glycol, giving olefines. Skeletal rearrangements were observed[1,2] of a type that might be useful in the synthesis of some terpenoid systems, and in any case are of interest in view of the basic reaction medium, unfavourable to carbonium–ion intermediates.

We now describe experiments designed to characterize this potentially useful reaction.

Since sulphinate anions are formed, electron-attracting groups were expected to increase its rate. Accordingly, attempts were made to prepare hydrazides of trifluoromethane- and 2,4-dinitrobenzenesulphonic acids, using the corresponding fluoride[3] and chloride,[4] repectively. With hydrazine, the former gave only gaseous products, and the latter, according to conditions, gave either the hydrazine arylsulphonate or 2,4-dinitrophenylhydrazine. Methanesulphonylhydrazine, however, was readily obtained, and proved on the whole a more satisfactory reagent (though actually rather slower reacting) than the aromatic derivative.

Acetone methanesulphonylhydrazone has pK_a ca. 8·5, as found by potentiometric titration. Accordingly, sulphonylhydrazones are very largely ionized under the basic conditions used for the reaction. The decomposition of the methane and *p*-toluene derivatives of cyclohexanone and camphor was studied kinetically, using a gas-burette to measure the evolved nitrogen; although results of high accuracy were not sought, good first-order plots were obtained, and rates were consistent from one run to another and independent of the surface area of the solid phase in contact with the solution.[5] A fourfold change in initial alkali concentration had no effect on the rate; as the hydrazone was present essentially as the anion, a reaction rate proportional to

[1] W. R. Bamford and T. S. Stevens, *J. Chem. Soc.* 4735 (1952).
[2] J. Elks, G. H. Phillipps, D. A. H. Taylor and L. J. Wyman, *J. Chem. Soc.* 1739 (1954).
[3] T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.* 173 (1956).
[4] H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch and O. Steinfort, *Chem. Ber.* **90**, 841 (1957).
[5] M. S. Newman and E. G. Caflisch, *J. Amer. Chem. Soc.* **80**, 862 (1958).

[anion] [H^+] is ruled out. The reaction may thus be classed as of mechanism E_1cb. There are, however, three general ways in which the conjugate anion of a sulphonylhydrazone might break down, in an initial, rate-determining stage:—

(a) to give an aliphatic diazo-compound, plus sulphinate;
(b) to give a carbene, plus either nitrogen and sulphinate or an unstable anion $\overline{N} = N \cdot SO_2R$, or
(c) to give an olefine directly, most plausibly via a cyclic transition state in which a β-hydrogen atom is removed by the departing sulphinate residue.

There is no doubt that mechanism (a) is often followed, as the aliphatic diazo-compounds can frequently be isolated. Bamford and Stevens[1] rejected the view that this was *always* the chosen route as the camphor derivative gave optically active camphene, whereas diazocamphane had been stated[6] to give tricyclene (which might decompose to camphene but must then give optically inactive material). We therefore chose cyclohexanone and camphor for kinetic study. Route (b) would require, in all probability, that the camphor derivative would react faster, because the formation of a carbene should be anchimerically assisted,[7] while route (c) would imply that the camphor derivative, apparently being unable to use the two β-hydrogen atoms to form the cyclic transition state for steric reasons, had to employ a different route and would thus be slower than the cyclohexanone derivative. In point of fact, the camphor and cyclohexanone derivatives reacted at virtually the same rate, and had, within experimental error, the same activation energies. This strongly suggests that the rate-determining stage precedes that at which skeletal rearrangement takes place in the camphor derivative; that is, it supports mechanism (a) even in this case. Accordingly, the evidence from product composition was re-examined, using gas-liquid chromatography. This at once revealed that the product from camphor was not pure camphene, but an 80 : 20 mixture with tricyclene. On the other hand, Meerwein and van Emster report[6a] the formation, along with tricyclene, of a small amount of camphene when diazocamphane decomposes. If it could be shown that changing the solvent markedly changed the camphene: tricyclene ratios in either reaction, the negative evidence against route (a) would be invalidated. As Table 1 shows, this was readily done.

In addition, the finding that diazocamphane and camphor methane and *p*-toluenesulphonylhydrazones gave these products in the same ratio would constitute positive evidence for such a mechanism. An attempt was made to use this test, employing 2-ethoxyethanol as solvent. Diazocamphane was readily obtained from N-nitroso-N-carbethoxybornylamine and sodium β-ethoxyethoxide,[6b] and allowed to decompose at various temperatures.

The tricyclene percentage rose with the temperature (Table 2), but it could not be raised to that obtained in the very slow reaction at high temperatures from the methanesulphonylhydrazone. The values attributed to temperatures of 100° and 135° were in reality representative of lower temperatures, as the rate of decomposition was comparable to that of heating; however, in spite of these limitations, we think that the results of Table 2 do add useful confirmatory evidence. Under all conditions investigated the methane- and toluenesulphonylhydrazones gave identical results.

[6a] H. Meerwein and K. van Emster, *Ber. Dtsch. Chem. Ges.* **53**, 1815 (1920); [b] U. Heubaum and W. A. Noyes, *J. Amer. Chem. Soc.* **52**, 5070 (1930).
[7] S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Course, D. Trifan and H. Marshall, *J. Amer. Chem. Soc.* **74**, 1127 (1952).

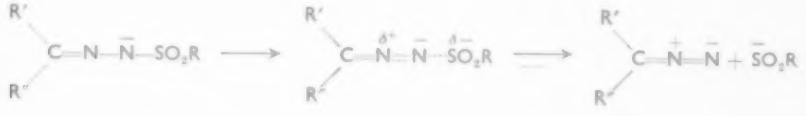
VOL. 7 1959

TABLE 1. PRODUCT FROM CAMPHOR SULPHONYLHYDRAZONE DECOMPOSITION

Hydrazone	Solvent	Temperature	% Tricyclene
Ts	Glycerol	132°	12
Ts	Ethylene glycol	124	15
Ts	Ethylene glycol	139	20
Ms	Ethylene glycol	139	21
Ts	Ethylene glycol	195	23
Ts	Trimethylene glycol	132	46
Ms	Diethylene glycol	139	53
Ts	Ethanolamine	132	91
Ts	2-Ethoxyethanol	132	92
Ms	Acetamide	181	97
Ts	Acetamide	181	97
Ms	Acetamide	156	98
Ts	Acetamide	156	99

The following abbreviations are employed throughout: Cm = camphor, Hx = cyclohexanone, Ts = toluene-*p*-sulphonyl, Ms = methanesulphonyl.

It remains to explain (a) the solvent effects on the rate of the rate-determining initial decomposition, and (b) the fact that the decomposition of diazocamphane gives the two hydrocarbons in a ratio that varies so much with solvent. Formally, the elimination involves an increase in polarity in the transition state:—



and would be expected to proceed faster in polar solvents. Actually the reverse is the case; but perhaps the system is so complex, in that in all stages hydrogen-bonded species predominate, that predictions would be intrinsically unreliable.

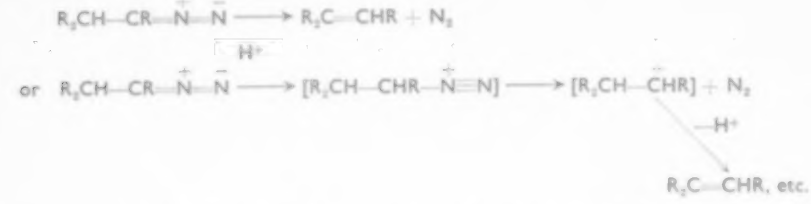
TABLE 2. VARIATION OF PRODUCT COMPOSITION WITH DECOMPOSITION TEMPERATURE FOR DIAZOCAMPHANE IN 2-ETHOXYETHANOL

Temperature	20°	52°	100°	135°
% Tricyclene	36	38	56	65%

The effect of solvent upon product composition is more interesting; generally, the formation of camphene is promoted by a high concentration of acidic protons (Cram *et al.*[8] have observed a similar effect on the steric course of aliphatic electrophilic substitution). Apparently—NH—groups are ineffective in this sense. The

[8] D. J. Cram, Private Communication.

simplest explanation is that a diazo-compound can decompose either without or with acid catalysis:—



In proton-rich solvents, the latter course predominates, and the sulphonyl-hydrazone decomposition then leads to products similar to those obtained in deamination with nitrous acid; whereas in, e.g. acetamide, most of the diazo-compound decomposes as such. In point of fact bornylamine does give mainly camphene, rather than tricyclene, with nitrous acid;[9] however, one would anticipate that if diazonium ions were indeed intermediates in, e.g., ethylene glycol, substitution products would be formed along with olefines. As Bamford and Stevens[1] reported a virtually quantitative yield of cyclohexene from the toluenesulphonylhydrazone of cyclohexanone in ethylene glycol, we repeated their experiment. They isolated the cyclohexene after transformation, via the dibromide, to the picrate of piperidinocyclohexene. We did not use this method, or try to weigh the volatile hydrocarbon, but noted that, either under our preferred conditions (methanesulphonylhydrazone at 156°) or theirs (toluene-*p*-sulphonylhydrazone at ca. 190°), *β*-cyclohexyloxyethanol was isolable in yields of 20–35 per cent. Although this implies a lower substitution/elimination ratio than that found for aqueous deamination at room temperature, the difference is no larger than would be expected.

EXPERIMENTAL

Treatment of 2,4-dinitrobenzenesulphonyl chloride with hydrazine hydrate. 2,4-Dinitrobenzenesulphonyl chloride[4] (5·3 g, 0·02 mole) in warm ethanol (25 ml) was added dropwise to an ice-cooled, well-shaken solution of hydrazine hydrate (2·5 g, 0·05 mole) in ethanol (25 ml). After standing 2 hr the precipitate was filtered off, and recrystallized from ethanol, giving *hydrazine 2,4-dinitrobenzenesulphonate* (1·4 g, m.p. (decomp) 155–160°), freely soluble in water. (Found: C, 25·8; H, 3·0; N, 20·4. $C_6H_6O_7N_4S$ requires: C, 25·7; H, 2·9; N, 20·0%).

Treatment of 2,4-dinitrobenzenesulphonyl chloride with anhydrous hydrazine. Anhydrous hydrazine (0·48 g, 0·015 mole) in N,N-dimethylformamide (5 ml) was added to the sulphonyl chloride (1 g, 0·0038 mole) in N,N-dimethylformamide (10 ml), the mixture turning deep red. Water (20 ml) was added, and after standing 1 hr, the product (0·53 g, m.p. 198°) was filtered off. This product was shown by mixed m.p., and comparison of infra-red spectra, to be 2,4-dinitrophenylhydrazine.

Methanesulphonyl hydrazine. To a vigorously stirred solution of hydrazine hydrate (108 g) in ethanol (50 ml) a solution of methanesulphonyl chloride (96 g) in ethanol (50 ml) was added dropwise (about 60 min), the reaction vessel being cooled in running water (12°). After stirring a further 15 min, ethanol was removed under reduced pressure until a homogeneous solution was obtained. This solution was acidified with phosphoric acid (to pH 5) to hold in the aqueous phase the unchanged hydrazine, and the required *hydrazine* was separated by continuous ether extraction (96 hr). On removal of ether, a syrup (n_D^{16} 1·497) was obtained, which slowly solidified on seeding (63·5 g, 68%, m.p. 49°). Recrystallization from ethyl acetate gave cubic crystals, m.p. 50·5°. (Found: C, 11·5; H, 5·5; N, 25·7. $CH_6O_2N_2S$ requires: C, 10·9; H, 5·5; N, 25·4%). (Seed crystals were obtained only after several weeks at 15°; decomposition prevented distillation even at 10^{-3} mm.)

[9] Von W. Huckel and F. Nerdel, *Liebigs Ann.* **528**, 57 (1937).

Acetone methanesulphonylhydrazone. Acetone (3 ml) was added to a solution of methanesulphonylhydrazine (2·2 g) in hot water (5 ml). On cooling, *acetone methanesulphonylhydrazone* (1·8 g, 61%) separated. Recrystallization from ethanol gave needles, m.p. 120°. (Found: C, 32·2; H, 6·7. $C_4H_{10}N_2O_2S$ requires: C, 32·0; H, 6·7%).

Titration of an N/100 aqueous solution of the sulphonylhydrazone with N/10 sodium hydroxide solution, using a Cambridge pH meter, gave the approximate value of pK_a as 8·5.

Camphor methanesulphonylhydrazone. Using the method of Bamford and Stevens,[1] methanesulphonylhydrazine (6·1 g), camphor (4·4 g) and 1% ethanolic hydrochloric acid (25 ml) were heated under reflux for 30 min, and cooled, when the *sulphonylhydrazone* separated (6·3 g, 60%, m.p. 126°). Recrystallization from ethanol gave needles, m.p. 129° (Found C, 54·1; N, 8·2; N, 11·4. $C_{11}H_{20}N_2O_2S$ requires: C, 54·05; H, 8·25; N, 11·5%).

Cyclohexanone methanesulphonylhydrazone. Methanesulphonylhydrazine (11 g) was dissolved in hot ethanol (50 ml) and cyclohexanone (10 ml) was added. On cooling and seeding, the *sulphonylhydrazone* separated (10·75 g, 60%). Recrystallization from ethanol gave needles, m.p. 103–104° (Found: C, 44·6; H, 7·4; N, 14·7. $C_7H_{14}N_2O_2S$ requires: C, 44·2; H, 7·4; N, 14·7%).

Kinetic investigations. For each run, the sulphonylhydrazone (ca. 0·003 mole) was added to 10 ml of reagent, this being, unless otherwise specified, a 1·3 N solution of sodium in ethylene glycol, the glycol having been purified by distillation over sodium. The reaction mixture was contained in a test-tube fitted with ground-glass joint, and was connected, via a water-condenser, to a simple gas-burette. The reaction vessel was heated by vapour-bath. First-order rate constants and activation energies were determined graphically, and are probably reliable to ±5% and ±2 kcal, respectively.

In addition to the results summarized in Table 3, the following observations were made: The rate of decomposition of camphor toluene-*p*-sulphonylhydrazone at 139° is given by $10^4k = 21 \pm 1$ sec^{-1}, when treated with 1·3 N reagent, 0·65 N reagent, or 0·325 N reagent; and the rate remains within these limits whether the reaction is carried out in the absence of added surface area, or in a tube packed with porous pot. In formamide solution, no visible reaction took place at 180°, whilst in 2 N aqueous sodium hydroxide, heated to ca. 135° in an autoclave, several hours were needed for appreciable reaction to take place.

TABLE 3. REACTION RATES

Hydrazone	Solvent	$10^4 k$ (sec^{-1})					E (kcal/mol)
		124°	132°	139°	156°	165°	
HxMs	Ethylene glycol			3·4	24	48	28
HxTs	Ethylene glycol		15	26	120		31
CmMs	Ethylene glycol		4·9	8·6	34	85	30
CmTs	Ethylene glycol		12	21	78	160	28
CmTs	Amyl alcohol	8·3	18				
CmTs	2-Methyl cyclohexanol				250		

Abbreviations as in footnote to Table 1.

Product composition investigations. The camphor sulphonylhydrazone (0·0015 mole) was mixed with a 1·3 N solution of sodium in the specified solvent (5 ml), the solvent having been purified by distillation over sodium. The reaction mixture was heated by vapour-bath until nitrogen evolution ceased. After cooling, water (5 ml) and pentane (2 ml) were added. After shaking, a portion of the pentane layer was withdrawn, and submitted to gas-liquid chromatography. By using a solution of silver nitrate in diethylene glycol[11] as stationary phase a clear separation was obtained between camphene and tricyclene. Early runs were carried out using a katharometer detector, but a flame ionisation detector was used for the later work, thus giving a higher sensitivity, and less trouble from the relative volatility of diethylene glycol at 80°, the column temperature used. In either case, it was

assumed that the area under the peak should be approximately proportional to the amount of hydrocarbon present, a reasonable assumption for isomeric compounds.

Diazocamphane. Ethyl bornylcarbamate[10] (4 g) in dry ether (20 ml) was cooled to −15°, and nitrogen sesquioxide (generated by the action of conc. nitric acid on arsenious oxide) was passed in until the solution was strongly coloured green. This solution was kept at −15° for a further 2 hr; it was then washed rapidly with water and saturated sodium hydrogen carbonate solution at 0°. It was immediately cooled to −60°, and the precipitated ice filtered off. After addition of 2-ethoxyethanol (15 ml), the required solvent for the next stage, the ether was removed at 0° under reduced pressure, and the resulting solution of the N-nitrosourethane kept at −60° until required.

To about 2·5 ml of this solution was added a 1·3 N solution of sodium β-ethoxyethoxide in 2-ethoxyethanol (2·5 ml). The solution became cherry-red, indicating the formation of diazocamphane. This was decomposed *in situ* by heating rapidly to the appropriate temperature, and maintaining it there until the colour had faded. After cooling, water (5 ml) and pentane (2 ml) were added, and a sample of the pentane extract used for the G.L.C. process. The results are outlined in Table 2.

β-Cyclohexyloxyethanol. Cyclohexanone methanesulphonylhydrazone (7·55 g) was dissolved in 1·3 N sodium in ethylene glycol solution (75 ml), and the mixture was heated by oil-bath (maximum bath-temperature 175°) until nitrogen evolution subsided (ca. 15 min). After cooling, water (100 ml), was added, and the mixture extracted with ether (25 + 4 × 15 ml). The extract was washed, dried and evaporated on the water-bath and the residue was distilled under reduced pressure, the β-cyclohexyloxyethanol (2·0 g, 35%, n_D^{20} 1·4630) distilling at 93–95° (11 mm). (Found: C, 66·5; H,11·1. $C_8H_{16}O_2$ requires: C, 66·6; H, 11·2%).

[10] A. Seville and R. H. Pickard, *J. Chem. Soc.* 686 (1904).
[11] B. W. Bradford, D. Harvey and D. E. Chalkey, *J. Inst. Pet.* **41**, 80 (1955).

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SULPHUR COMPOUNDS IN THE KEROSINE BOILING RANGE OF MIDDLE EAST DISTILLATES

OCCURRENCE OF A BICYCLIC THIOPHENE AND A THIENYL SULPHIDE

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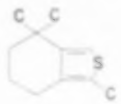
Abstract—A bicyclic thiophene, 1,4,4-trimethyl-4,5,6,7-tetrahydroisothianaphthene, and a thienyl sulphide, methyl 3, 4, 5-trimethyl-2-thienyl sulphide, have been isolated from a concentrate of sulphur compounds obtained in the refining of a Middle East kerosine. The structures of these compounds have been established.

IN recent years numerous investigations have been carried out into the nature of sulphur compounds in petroleum, particularly in distillates. The major components present in the gasoline range are thiols, alkane sulphides and cyclic sulphides[1–4] whilst in the kerosine boiling range we have shown[5,6] the additional presence of polycyclic sulphides and alkylthiophenes. Confirmation of the presence of alkylthiophenes in the lower boiling distillates has been afforded by the work of the American Petroleum Institute Research Project 48[7] which has conclusively identified thiophene and its 2-methylderivative. Considerably less is known of the sulphur compounds in the higher boiling distillates, e.g. gas oil and lubricating oil, and attention is now being directed toward materials in this boiling range. Unpublished work in these laboratories indicates that these sulphur compounds are predominantly thiophenic in character and this observation is substantiated by the work of Lumpkin and Johnson[8] who conclude from mass spectrometric data that the predominant type of sulphur compound is based on the thianaphthene ring, as well as by the data reported by Drushell and Miller.[9] In addition it should be pointed out that Cook *et al.*[10] have isolated three sulphur compounds, possessing a thiophene ring from a Kuwait gas oil.

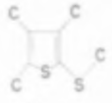
Examination of the fractions obtained by us from the kerosine extract tar oil previously described[5,6] has therefore been concentrated upon the higher boiling materials with particular reference to the thiophenic compounds and other non-aliphatic sulphur compounds in the hope that identification of individual compounds

[1] R. Emmott, *J. Inst. Petroleum* **39**, 695 (1953).
[2] F. Challenger, *Manuf. Chem.* **25**, 151 (1954).
[3] C. J. Thompson, H. J. Coleman, H. T. Rall and H. M. Smith, *Analyt. Chem.* **27**, 175 (1955).
[4] H. J. Coleman, N. G. Adams, B. H. Eccleston, R. L. Hopkins, L. Mikkelsen, H. T. Rall, D. Richardson, C. J. Thompson and H. M. Smith, *Analyt. Chem.* **28**, 1380 (1956).
[5] S. F. Birch, T. V. Cullum, R. A. Dean and R. L. Denyer, *Industr. Engng. Chem.* **47**, 240 (1955).
[6] S. F. Birch, T. V. Cullum and R. A. Dean, *Chemical and Engineering Data Series* **3**, 359 (1958).
[7] C. J. Thompson, H. J. Coleman, L. Mikkelsen, D. Yee, C. C. Ward and H. T. Rall, *Analyt. Chem.* **28**, 1384 (1956).
[8] H. E. Lumpkin and B. H. Johnson, *Analyt. Chem.* **26**, 1719 (1954).
[9] H. V. Drushell and J. F. Miller, *Analyt. Chem.* **30**, 1271 (1958).
[10] J. W. Cook, W. Carruthers and D. L. Woodhouse, *Brit. Med. Bull.* **14**, 132 (1958).

may be of assistance in the examination of those present in the higher boiling ranges. As a result we have identified in the fractions boiling around 250° two sulphur compounds possessing structures of a type not previously identified in naturally occurring materials viz. 1,4,4-trimethyl-4,5,6,7-tetrahydroisothianaphthene (I) and methyl 3,4,5-trimethyl-2-thienyl sulphide (II). It must be appreciated that these compounds



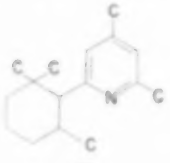
I



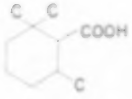
II

have been isolated by a combination of physical and chemical methods from a spent refining agent but we believe[5] that they have survived unchanged from the original petroleum distillate.

The identification of the thienyl sulphide is, as far as we know, the first occasion on which it has been demonstrated that petroleum contains sulphur compounds possessing more than one sulphur atom per molecule, apart from vicinal disulphides, which appear to arise very largely if not completely from the oxidation of mercaptans during processing of the crude. The immediate implications of this discovery are quite apparent when it is realized that the tentative attempts to analyse higher boiling fractions have always been based on the assumption that only one sulphur atom is present per molecule. Further consequences, e.g. the effect on the stability of petroleum products and on desulphurization processes, must await an evaluation of the percentage contribution of this type of sulphur compound and further study of its chemistry. By analogy with the sulphides the discovery of the bicyclic thiophene is not surprising since there appears to be a tendency in the sulphur compounds for an increase in the number of rings per molecule to take place with increase in boiling point, rather than for the length of chains to increase. One interesting point in the structure of I is its striking analogy with the pyridine (III) and acid (IV) which have been isolated from Californian distillates[11,12] and its slight similarity to Vitamin A. These analogies may



III



IV

be compared with those already pointed out for hydrocarbons and sulphur compounds[6] and may possibly be of some assistance in considerations of the origin of petroleum.

Isolation and structure determination

The preparation of the fraction (XXVII b.p. 245–249°) has been previously described,[5,6] as has the extraction of this fraction with aqueous mercuric acetate solution to yield a sulphide fraction, which has been shown to consist of mono- and poly-cyclic sulphides, a solid acetoxymercurithiophene and an unextracted portion.

[11] B. Shive, S. M. Roberts, R. I. Mahan and J. R. Bailey, *J. Amer. Chem. Soc.* **64**, 909 (1942).
[12] W. O. Ney, W. W. Crouch, C. E. Rannefeld and H. L. Lochte, *J. Amer. Chem. Soc.* **65**, 770 (1943).

The latter was assumed to consist of tetra-alkylthiophenes together with small amounts of aromatic hydrocarbons and oxygenated materials.[5] The acetoxymercurithiophene after crystallization to constant melting point analysed as the monoacetoxy mercuri-derivative of a trialkylthiophene. However, analysis of the thiophene itself gave the formula $C_{11}H_{16}S$ and this together with its high refractive index, n_D^{20} 1·5393, suggested the presence, in the molecule, of a naphthene ring. Desulphurization of the thiophene was carried out by the normal technique[6] and the product and the original thiophene were examined by mass, infra-red, ultra-violet and proton magnetic resonance spectrometry. It was known, from a bromine number determination, that the desulphurization product contained an appreciable amount of olefinic material and gas-liquid chromatography indicated that this was 50 per cent of the mixture. Infra-red and proton magnetic resonance spectra demonstrated that the olefin had no hydrogen atoms attached to the doubly bonded carbon atoms and the mass spectrum confirmed that the olefin content was of the order of 50 per cent (assuming equal sensitivities for the olefin and the naphthene). Further information obtained was the presence of an α-methyl group on the thiophene (*m/e* peak at 59), one hydrogen atom attached to the thiophene ring (proton magnetic resonance) and an indication of the presence of a *gem*-dimethyl group (infra-red doublet at 7·22 μ and 7·32 μ) in the thiophene. The presence of this *gem*-dimethyl group in the desulphurization product was confirmed by the existence of a main band at 7·26 μ with shoulders at 7·22 μ and 7·32 μ in the infra-red spectrum of the naphthene, which was separated from the olefin by the Fluorescent Indicator Adsorption technique.[13]

From all these data it appeared probable that the thiophene possessed a methyl group and a hydrogen atom in the α-positions and that a naphthene ring with a *gem*-dimethyl group was fused in the β-positions, but it was not possible to say whether this was a five-membered ring with three methyl substituents or a six-membered with two. This problem was resolved by comparison of the dehydrogenation of the naphthene with that of model compounds, when it was shown to behave as a six-membered ring with a *gem*-dimethyl group and to yield methane and ethyl-2,3-dimethylbenzene. Final proof of the structure (I), which was now clearly indicated was obtained by the synthesis of ethyl-2,3,3-trimethylcyclohexane (IX) and its identification with the naphthene formed on desulphurization of I. The synthesis of IX was carried out by normal procedures from 3,3-dimethyl-2-carbethoxycyclohexanone (V),[14] via 2,3,3-trimethylcyclohexanone (VI), ethyl-2,3,3-trimethylcyclohexanol (VII) and ethyl-2,3,3-trimethylcyclohexenes (mixed olefins) (VIII).

The occurrence of the bicyclic thiophene suggested that a tetrasubstituted analogue might be present in the portion not extracted by mercuric acetate solution and this was accordingly investigated. Fractionation, by gradient elution chromatography on silica gel, gave appreciable separation and a pronounced refractive index peak (n_D^{20} 1·5600) occurred in the material eluted by a cyclohexane/benzene mixture. The sulphur content (32 per cent) of the fraction of this refractive index and the *m/e* ratio (172) of a large peak in the mass spectrum suggested the presence of a thienyl sulphide. Gas-liquid chromatographic and infra-red spectroscopic data were obtained, the former suggested that one component accounted for 70–80 per cent of the fraction

[13] *ASTM Standards on Petroleum Products and Lubricants (with Related Information)*. D. 1319–56T. American Society for Testing Materials, Philadelphia 3, Pa. (1956).
[14] U. Steiner and B. Willhalm, *Helv. Chim. Acta* **35**, 1752 (1952).

but no conclusion could be drawn from the latter. Examination of the desulphurization product by gas-liquid chromatography and mass spectrometry demonstrated that it was a mixture of a C_7 paraffin and olefin possibly 2,3-dimethylpentane or 3-methylhexane and 2,3-dimethylpentene-1. Since the thienyl sulphide was probably tetra-substituted (unreactive toward mercuric acetate solution) the only two feasible compounds that could satisfy these requirements appeared to be methyl 3,4,5-trimethyl-2-thienyl sulphide (II) and methyl 2,4,5-trimethyl-3-thienyl sulphide and these were accordingly synthesized. Comparison of the infra-red spectra of these compounds with that of the fraction n_D^{20} 1·5600 showed that the compound present was II, the only significant adsorption present in the spectrum not accounted for by this compound (13·55 μ and 14·31 μ) being attributable to aromatic hydrocarbons.

The syntheses of the two thienyl sulphides also followed normal procedures, from 2,3,4-trimethylthiophene and 2,3,5-trimethylthiophene.

EXPERIMENTAL*

Spectra. The infra-red† spectra were determined on a Grubb Parsons Double Beam Recording Infra-red Spectrometer; the ultra-violet spectra† on a Carey Recording Spectrophotometer Model 11, the mass spectra on a Metropolitan Vickers M.S.2. Mass Spectrometer and the nuclear magnetic resonance spectra on a Varian Nuclear Magnetic Resonance Spectrometer.

Isolation and characterization of the bicyclic thiophene (I)

The crude *acetoxymercurithiophene* isolated from fraction XXVII of the tar oil, b.p. 245–249°/760 was crystallized from acetone and methanol, m.p. 163–165°. A total of 38·5 g of pure derivative was obtained (Found: C, 35·8; H, 4·2; S, 7·7. $C_{15}H_{16}O_2SHg$ requires: C, 35·6; H, 4·1; S, 7·3%). A suspension of this derivative in 5 N hydrochloric acid was refluxed and the *thiophene* (12 g) which was separated from the distillate using an oil/water separator, had the following physical properties b.p. 66–70°/0·3 mm, m.p. 21–22°, n_D^{20} 1·5393 (supercooled liquid) (Found: C, 72·9; H, 8·8; S, 17·8. $C_{11}H_{16}S$ requires: C, 73·3; H, 9·0; S, 17·8%). By reaction of the acetoxymercuriderivative with sodium chloride, a *chloromercuri*-derivative was formed, m.p. 197–199° from benzene/ethanol (Found: C, 31·9; H, 3·7; S, 7·8; Cl, 8·4. $C_{11}H_{15}SClHg$ requires: C, 31·8; H, 3·6; S, 7·7; Cl, 8·5%). A *mercury dithienyl*, m.p. 179–180° from benzene/ethanol, was obtained by reaction of the acetoxymercuri-derivative with sodium iodide (Found: C, 47·0; H, 5·4; S, 11·4. $C_{22}H_{30}S_2Hg$ requires: C, 47·3; H, 5·4; S, 11·5%). Gas-liquid chromatography of the thiophene showed one peak only of retention volume 41·8 relative to n-octane with a silicone oil as stationary phase at 134°, and of 0·68 relative to n-hexadecane with Apiezon grease L as stationary phase at 245°. The infra-red spectrum showed absorption at 7·22 μ and 7·32 μ attributed to a *gem*-dimethyl group, the mass spectrum a significant peak at *m/e* 59 indicative of an α-methyl group on the thiophene ring and a parent peak at *m/e* 180, and the nuclear magnetic resonance spectrum a peak attributable to a proton on the thiophene ring having an area approximately 1/16 of the total proton peaks.

Desulphurization of the bicyclic thiophene (I)

Treatment of the thiophene with Raney nickel in Carbitol (the monoethyl ether of diethyleneglycol) by the usual technique[6] gave a 75 per cent yield of product, n_D^{20} 1·4586. Gas-liquid chromatography showed the presence of two equal peaks of retention volumes 5·80 and 5·95 relative to n-octane with a silicone oil stationary phase at 130°. The latter was shown to be the naphthene and the former the cyclic olefin by comparison with the relative retention volumes of the separated hydrocarbons (*vide infra*). The olefin and naphthene had retention volumes of 5·6 and 6·6 respectively relative to n-octane with n-tetratriacontane as stationary phase at 145°. Although the bromine number of an olefin $C_{12}H_{26}$ would be expected to be 105, that of the desulphurization product was 115. The components

* All melting points are corrected. Some of the analyses were performed by Dr. Ing. A. Schoeller of Kronach/Oberfranken, Bambergerstrasse 20, Germany.

† These spectra are being submitted for inclusion in the American Petroleum Institute's Catalogue of Spectral Data.

of the desulphurization product (1·10 g) were separated by the Fluorescent Indicator Adsorption technique[13] modified by continuing the isopropanol elution to displace the bands from the column. Four fractions were collected, (1) 0·50 g, colourless material, (2) 0·10 g, an intermediate fraction at the junction of the colourless and yellow bands of material, (3) 0·42 g, yellow coloured material, (4) 0·13 g, an intermediate fraction between (3) and the isopropanol. Fraction (1) was shown by mass spectrometry to be the naphthene (*m/e* 154 : *m/e* 152 : 580 : 1) and fraction (3) to be the olefin with a small amount of naphthene still present (*m/e* 152 : *m/e* 154 : 36 : 1). The results indicate that the desulphurization product was a 1 : 1 mixture of naphthene and olefin—which must have an anomalous bromine number. The infra-red spectrum of the naphthene showed large absorption at 7·26 μ with shoulders at 7·22 μ and 7·32 μ suggesting the presence of a *gem*-dimethyl group. The fact that no absorption was observed at 3·29 μ in the infra-red spectrum of the olefin demonstrated the absence of hydrogen atoms attached to the doubly bonded carbon atoms and this was confirmed by the ultra-violet iodine absorption complex method.[13] The nuclear magnetic resonance spectrum of the desulphurization product had no peak corresponding to a proton on the doubly bonded carbon atoms.

Dehydrogenation of the naphthene (IX)

A commercial platinum on alumina catalyst (200 g) was dried at 425° for 30 min and then stirred with a solution of sodium acetate trihydrate (32 g in 300 ml water). After decanting off the excess aqueous phase, the catalyst was heated in an oven at 150–170° (7 hr) and finally in a current of hydrogen at 500°. This catalyst was used to study the dehydrogenation of various model compounds in an atmosphere of hydrogen at 350° and a space velocity of 0·5 v/v per hr. Analyses of the products were carried out by a combination of gas-liquid chromatography and mass spectrometry and the results together with those from the naphthene are given below.

Compound	Conversion to aromatic (mol %)
1,1,3-Trimethylcyclopentane	3 to 4
n-Propylcyclopentane	>5
1,1-Dimethylcyclohexane	30
Naphthene (IX)	33
cis-Ethyl-2-methylcyclohexane	85

The evolution of methane during the dehydrogenation of the naphthene was demonstrated by taking a sample of the effluent gases; the methane content of the effluent gases was 12·6 per cent w/w compared with 0·2 per cent w/w in an experiment with benzene. One of the peaks in the gas-liquid chromatogram of the product from the dehydrogenation of the naphthene had the same retention volume as that of ethyl-2,3-dimethylbenzene (8·9 relative to n-octane with a silicone oil stationary phase at 130°). The material having this retention volume was collected and its ultra-violet spectrum obtained; ethyl-2,3-dimethylbenzene was the only C_{10} aromatic with this spectrum.

Synthesis of ethyl-2,3,3-trimethylcyclohexane (IX)

3,3-Dimethyl-2-carbethoxycyclohexanone (V), was prepared in 23 per cent yield from mesityl oxide as previously described,[14] b.p. 69–73°/0·3 mm, n_D^{20} 1·4638, 2,4-dinitrophenylhydrazone m.p. 117° (Steiner and Willhalm[15] quote m.p. 116–116·5°). The sodium salt of V was reacted with methyl iodide by a modification[16] of the method of Linstead and Meade to give a 75 per cent yield of 2,3,3-*trimethyl-2-carbethoxycyclohexanone*, b.p. 105–114°/0·3 mm, n_D^{20} 1·4657, retention volume 1·57 relative to naphthalene with Apiezon grease N as stationary phase at 197°. The 2,4-*dinitrophenylhydrazone* had m.p. 119·5–120° (from ethanol) (Found: C, 55·2; H, 6·4; N, 14·1. $C_{18}H_{24}O_6N_4$ requires: C, 55·1; H, 6·2; N, 14·3%). The *semicarbazone* had m.p. 185·5–186·5° (from ethanol)

[15] D. R. Long and R. W. Neuzil, *Analyt. Chem.* **27**, 1110 (1955).
[16] S. F. Birch, R. A. Dean and E. V. Whitehead, *J. Org. Chem.* **23**, 783 (1958).

(Found: C, 58·1; H, 8·8; N, 15·8. $C_{12}H_{23}O_3N_3$ requires: C, 58·0; H, 8·6; N, 15·6%). Decarboxylation and hydrolysis of the keto-ester (8·8 g) was carried out by refluxing it with a mixture of glacial acetic acid (60 ml) and conc. hydrochloric acid (40 ml).[17] The course of decarboxylation was followed by gas-liquid chromatography, and was only 80 per cent complete after 200 hr and still not complete after 344 hr when the reaction was stopped. The crude product was found to be a mixture of 2,3,3-trimethyl-2-carbethoxycyclohexanone, 2,3,3-trimethylcyclohexanone (VI) and 3,3-dimethylcyclohexanone. Pure VI was isolated by gas-liquid chromatography using a commercial alkylarylsulphonate detergent as stationary phase[18] at 138° (the charge was ca. 1·5 g per run using a column 15 m long and 2·2 cm dia.). Yield 60 per cent, b.p. 63°/8 mm, n_D^{20} 1·4557, retention volume 5·22 relative to n-octane with n-tetratriacontane as stationary phase at 145°, oxime m.p. 92–93° (from aqueous ethanol) (Crossley and Renouf[19] quote m.p. 95°). The ketone (VI, 1·85 g) in ether (10 ml) was reacted in the usual way with excess ethylmagnesium bromide (from magnesium 1·3 g). The *alcohol* (VII), retention volume 14·2 relative to n-octane with n-tetratriacontane as stationary phase at 145°, was used without further purification for the next step in the synthesis. (Gas-liquid chromatography indicated the presence of a small amount of ether and a small amount of VI (not more than 2 per cent of the product). Dehydration was carried out by heating the alcohol with naphthalene-2-sulphonic acid[20] at 150°. The mixture of olefins (VIII) was extracted with ether, dried with potassium carbonate and finally redistilled. Yield 60 per cent, b.p. 85°/18 mm, n_D^{20} 1·4642. Examination of the product by gas-liquid chromatography showed two incompletely separated peaks of retention volumes 5·6 and 6·1 respectively relative to n-octane with n-tetratriacontane as stationary phase at 145°. The infra-red spectrum demonstrated the presence of olefins with protons on the carbon atoms attached by the double bonds and this was confirmed by the ultra-violet iodine complex method[15] (the peak with retention volume 6·1 is presumably due to this type of olefin). VIII (0·55 g) was heated in Carbitol with Raney nickel at 100° for 90 min, (this method of hydrogenation was chosen to increase the probability of the naphthene having the same stereochemical configuration (which is unknown) as that produced by the desulphurization process from the thiophene), and the product (0·16 g), n_D^{20} 1·4562, worked up in the usual way. Gas-liquid chromatography showed the presence of two peaks of retention volumes 5·6 and 6·6 respectively relative to n-octane with n-tetratriacontane as stationary phase at 145°. No peak of retention volume 6·1 could be seen (limit of detection 5 per cent of the sample). The product was separated by the Fluorescent Indicator Adsorption technique into naphthenic (0·03 g) and olefinic (0·05 g) fractions. The infra-red spectrum of the former was identical with that of the naphthene isolated from the desulphurization product of the thiophene. The latter was shown by spectroscopic methods to be fully alkylated and must therefore be ethyl-2,3,3-trimethylcyclohexene-1.

Isolation and desulphurization of the thienyl sulphide (II)

The unextracted portion from fraction XXVII of the tar oil after treatment with aqueous mercuric acetate solution was exhaustively extracted with further aqueous mercuric acetate until only traces of sulphides were extracted, it was then distilled under reduced pressure, wt. 39 g, n_D^{20} 1·5211, thiophene content 70–80 per cent (ultra-violet spectroscopy). Part of this material (11 g) was given a preliminary chromatographic separation using silica gel (213 g, 28–200 mesh) with pentane/benzene/ethanol as successive eluants. A portion (5·9 g, n_D^{20} 1·5328) of the benzene-eluted material was chromatographed over silica gel (186 g), pre-wetted with cyclohexane, using the technique of gradient elution with a stirred mixing chamber,[21] cyclohexane (100 ml), benzene (150 ml) and ethanol (45 ml) being used as eluants. Solvents were removed by distillation and the residues combined, as indicated by refractive index, to give the fractions listed in the table on p. 317.

An infra-red spectrum on the fraction n_D^{20} 1·5359 indicated a very complex mixture but showed absorption at 13·55 μ and 14·31 μ attributable to aromatic hydrocarbons. This absorption was absent in a sample that had been washed with conc. sulphuric acid, confirming this assignment. An infra-red spectrum of the fraction n_D^{20} 1·5600, sulphur content 32·0 per cent w/w, was recorded, as

[17] R. H. Martin and Sir R. Robinson, *J. Chem. Soc.* 491 (1943).
[18] D. H. Desty and C. L. A. Harbourn, Divisions of Petroleum and Analytical Chemistry, *Symposium on Advances in Gas Chromatography* p. D-157. 132nd Meeting, ACS, New York, Sept. (1957).
[19] A. W. Crossley and N. Renouf, *J. Chem. Soc.* **99**, 1101 (1911).
[20] E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson, *J. Amer. Chem. Soc.* **61**, 1057 (1939).
[21] D. W. Bannister, C. S. G. Phillips and R. J. P. Williams, *Analyt. Chem.* **26**, 1451 (1954).

Solvents in eluant	Total volume of eluant (ml)	Residue	
		Wt. (g)	n_D^{20}
Cyclohexane	47	1·25	1·5200
Cyclohexane/benzene	68	2·60	1·5359
Cyclohexane/benzene	88	0·75	1·5600
Cyclohexane/benzene	173	0·50	1·5445–1·4969
Cyclohexane/benzene/ethanol	178	0·15	1·5100
Cyclohexane/benzene/ethanol	350	0·10	—

was also its mass spectrum which showed a large peak at *m/e* 172 (II has a molecular weight of 172). The gas-liquid chromatogram had a peak (accounting for approximately 70 per cent of the sample) with a retention volume of 3·85 relative to n-dodecane with a solid synthetic detergent as stationary phase[15] at 245°. Desulphurization of the fraction was carried out by the normal method[6] and the gas-liquid chromatogram obtained. Peaks were present corresponding in retention volume to heptanes but no definite assignment could be made and no quantitative estimate was possible. Other minor peaks were present in the region of hydrocarbons formed from sulphur compounds possessing one sulphur atom per molecule and some peaks were present of retention volume comparable with the original sulphur compound fraction suggesting the presence of non-sulphur compound impurities. The cracking pattern of the desulphurization product indicated that a heptene, possibly, 2,3-dimethylpentene-1 was present as well as heptanes.

Synthesis of methyl 3,4,5-trimethyl-2-thienyl sulphide (II)

2,3,4-Trimethylthiophene (5·6 g, 0·044 mole) was dissolved in benzene (40 ml) and mercuric oxide (7·9 g, 0·037 mole) and iodine (11·6 g, 0·091 g atom) were added alternately in small portions with vigorous stirring.[22] Mercuric iodide was filtered off and from the filtrate there was obtained, by distillation, 2-iodo-3, 4, 5-trimethylthiophene (9 g) in 79 per cent yield, b.p. 134°/20 mm. The thienylmagnesium iodide was prepared[23] by the reaction of the iodo-compound (9 g, 0·036 mole) with magnesium (1 g, 0·041 g atom) in ether under a nitrogen atmosphere, sulphur (1·2 g, 0·038 g atom) was added, with stirring, the reaction mixture refluxed for 2 hr and decomposed with dil. HCl. The trimethylthiophenethiol was extracted from the ether with 4 N caustic soda solution (20 ml), ethanol (25 ml) and methyl iodide (5·1 g, 0·036 mole) were added to the alkaline layer and the solution was refluxed for 2 hr. Dilution of the reaction mixture with water, extraction with pentane and distillation of the extract gave II in 17 per cent overall yield, b.p. 124–126°/18 mm, n_D^{20} 1·5688 (Found: C, 55·6; H, 7·1; S, 37·5. $C_8H_{12}S_2$ requires: C, 55·8; H, 7·0; S, 37·2%). The ethanol solution from the Grignard reaction, after extraction with alkali, was evaporated to dryness and the residue on crystallization from cyclohexane gave the *di-(3,4,5-trimethyl-2-thienyl) disulphide* (0·8g) as yellow crystals m.p. 89·5–90·5° (Found: C, 53·6; H, 6·2; S, 40·5. $C_{14}H_{18}S_4$ requires: C, 53·5; H, 5·8; S, 40·8%).

Synthesis of methyl 2,4,5-trimethyl-3-thienyl sulphide

2,3,5-Trimethylthiophene (1·05 g, 0·0084 mole) was heated at 40° with sulphuric acid (4·05 g, 0·042 mole) for 1 hr, the cooled reaction mixture was poured into water and the aqueous solution was neutralized with sodium hydroxide and evaporated to dryness under reduced pressure. The sodium thiophenesulphonate (0·95 g), 50 per cent yield, was isolated by extraction of the dry solid with ethanol; a total of 3 g was prepared by this method. Conversion to the sulphonyl chloride was effected by heating the sodium salt with phosphorus oxychloride at 130–150° for 2·5 hr and the sulphonyl chloride was isolated by addition of the reaction mixture to water, followed by extraction with ether, (1·2 g), 40 per cent yield, b.p. 154°/15 mm. This sulphonyl chloride (1·2 g, 0·0053 mole) was reduced in the usual manner[24] with lithium aluminium hydride (1·2 g, 0·03 mole), the product

[22] W. Minnis, *Organic Syntheses* Coll. Vol. II, p. 357. John Wiley, New York (1943).
[23] P. D. Caesar and P. D. Branton, *Industr. Engng. Chem.* **44**, 122 (1952).
[24] C. S. Marvel and P. D. Caesar, *J. Amer. Chem. Soc.* **72**, 1033 (1950).

was extracted into an aqueous solution of sodium hydroxide and reacted with methyl iodide (*vide supra*) to give the required sulphide (0·45 g), 53 per cent yield, b.p. 120°/18 mm, n_D^{20} 1·5640.

The infra-red spectrum of this sulphide was obtained and none of it could be detected in the thienyl sulphide fraction of the tar oil (limit of detection ca. 3 per cent).

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7
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